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(54) Title: M_3MUSCARINIC ACETYLCHOLINE RECEPTOR ANTAGONISTS

(57) Abstract: M_3 Muscarinic Acetylcholine Receptor Antagonists and methods of using them are provided.

M_3 MUSCARINIC ACETYLCHOLINE RECEPTOR ANTAGONISTS

FIELD OF THE INVENTION

This invention relates to novel thiazole aniline compounds, pharmaceutical compositions, processes for their preparation, and use thereof in treating M_3 muscarinic acetylcholine receptor mediated diseases.

BACKGROUND OF THE INVENTION

Acetylcholine released from cholinergic neurons in the peripheral and central nervous systems affects many different biological processes through interaction with two major classes of acetylcholine receptors – the nicotinic and the muscarinic acetylcholine receptors. Muscarinic acetylcholine receptors (mAChRs) belong to the superfamily of G-protein coupled receptors that have seven transmembrane domains. There are five subtypes of mAChRs, termed M_1-M_5, and each is the product of a distinct gene. Each of these five subtypes displays unique pharmacological properties. Muscarinic acetylcholine receptors are widely distributed in vertebrate organs, and these receptors can mediate both inhibitory and excitatory actions. For example, in smooth muscle found in the airways, bladder and gastrointestinal tract, M_3 mAChRs mediate contractile responses. For review, please see (1).

Muscarinic acetylcholine receptor dysfunction has been noted in a variety of different pathophysiological states. For instance, in asthma and chronic obstructive pulmonary disease (COPD), inflammatory conditions lead to loss of inhibitory M_2 muscarinic acetylcholine autoreceptor function on parasympathetic nerves supplying the pulmonary smooth muscle, causing increased acetylcholine release following vagal nerve stimulation. This mAChR dysfunction results in airway hyperreactivity mediated by increased stimulation of M_3 mAChRs. Similarly, inflammation of the gastrointestinal tract in inflammatory bowel disease (IBD) results in M_3 mAChR-mediated hypermotility (3). Incontinence due to bladder hypercontractility has also been demonstrated to be mediated through increased stimulation of M_3 mAChRs. Thus the identification of subtytpe-selective mAChR antagonists may be useful as therapeutics in these mAChR-mediated diseases.

Despite the large body of evidence supporting the use of anti-muscarinic receptor therapy for treatment of a variety of disease states, relatively few anti-

muscarinic compounds are in use in the clinic. Thus, there remains a need for novel compounds that are capable of causing blockade at M_3 mAChRs. Conditions associated with an increase in stimulation of M_3 mAChRs, such as asthma, COPD, IBD and urinary incontinence would benefit by compounds that are inhibitors of mAChR binding.

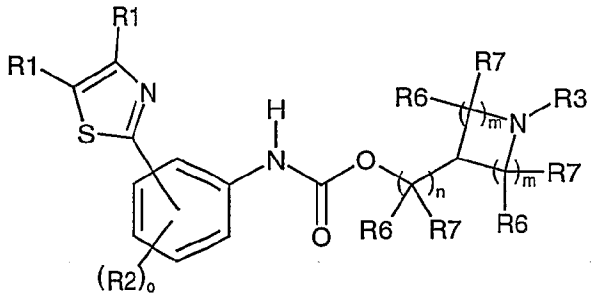
SUMMARY OF THE INVENTION

This invention provides for a method of treating a muscarinic acetylcholine receptor (mAChR) mediated disease, wherein acetylcholine binds to an M_3 mAChR and which method comprises administering an effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

This invention also relates to a method of inhibiting the binding of acetylcholine to its receptors in a mammal in need thereof which comprises administering to aforementioned mammal an effective amount of a compound of Formula (I).

The present invention also provides for the novel compounds of Formula (I), and pharmaceutical compositions comprising a compound of Formula (I), and a pharmaceutical carrier or diluent.

Compounds of Formula (I) useful in the present invention are represented by the structure:



(I)

wherein:

R1 is independently selected from the group consisting of hydrogen, halogen, NR_6R_7, OH, OR_a, $C(O)R_a$, $NR_aC(O)OR_a$; $OC(O)NR_6R_7$; $NR_9C(O)R_a$; $C(O)NR_6R_7$;

C(O)OH; $C(O)OR_a$; NHS(O)2Ra, C_{1-5}alkyl, aryl, C_{1-4}alkylaryl, C_{2-4}alkenyl; C_{2-4}alkenylaryl; cycloalkyl, C_{1-5} alkylcycloalkyl, heteroaryl, C_{1-4}alkylheteroaryl, C_{2-4} alkenylheteroaryl, heterocyclic, C_{1-4}alkyl heterocyclic, and a C_{2-4}alkenyl moiety heterocyclic, which, when feasible, may be optionally substituted independently by a substituent selected from the group consisting of halogen, nitro, C_{1-5}alkyl, amino, mono or di-C_{1-4} alkyl substituted amine, OR_a, $C(O)R_a$, $NR_aC(O)OR_a$, $OC(O)NR_6R_7$, hydroxy, $NR_9C(O)R_a$, $S(O)_mR_a$, $C(O)NR_6R_7$, C(O)OH, $C(O)OR_a$, $S(O)_2NR_6R_7$, and $NHS(O)_2R_a$; or two R1 moieties together may form a 5 to 6 membered saturated or unsaturated ring; and wherein the alkyl, aryl, arylalkyl, heteroaryl, heteroaryl alkyl, heterocyclic, heterocyclicalkyl groups may be optionally substituted;

R2 is selected from the group consisting of hydrogen, halogen, nitro, cyano, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy, halosubstituted C_{1-10} alkoxy; azide, $(CR_8R_8)qS(O)_tR_a$, $(CR_8R_8)qOR_a$, hydroxy, hydroxy substituted C_{1-4}alkyl, aryl, aryl C_{1-4} alkyl, aryloxy; arylC_{1-4} alkyloxy, aryl C_{2-10} alkenyl, heteroaryl, heteroarylalkyl, heteroaryl C_{1-4} alkyloxy, heteroaryl C_{2-10} alkenyl, heterocyclic, heterocyclic C_{1-4}alkyl, heterocyclicC_{2-10} alkenyl, $(CR_8R_8)qNR_4R_5$, C_{2-10} alkenyl $C(O)NR_4R_5$, $(CR_8R_8)qC(O)NR_4R_5$, $(CR_8R_8)q$ $C(O)NR_4R_{10}$, $S(O)_3R_8$, $(CR_8R_8)qC(O)R_{11}$, C_{2-10} alkenyl$C(O)R_{11}$, $(CR_8R_8)qC(O)OR_{11}$, C_{2-10}alkenyl$C(O)OR_{11}$, $(CR_8R_8)qOC(O)R_{11}$, $(CR_8R_8)qNR_4C(O)R_{11}$, $(CR_8R_8)q$ $NHS(O)_2R_{13}$, $(CR_8R_8)q$ $S(O)_2NR_4R_5$, $(CR_8R_8)qC(NR_4)NR_4R_5$, and $(CR_8R_8)q$ $NR_4C(NR_5)R_{11}$; or two R2 moieties together may form a 5 to 6 membered saturated or unsaturated ring; and wherein the alkyl, aryl, arylalkyl, heteroaryl, heteroaryl alkyl, heterocyclic, heterocyclicalkyl groups may be optionally substituted;

R3 is independently selected from the group consisting of hydrogen, C_{1-5}alkyl, aryl, C_{1-4}alkylaryl, C_{2-4}alkenyl, C_{2-4}alkenylaryl, C_{1-5} alkylcycloalkyl, cycloalkyl, cycloalkyl C_{1-5} alkyl, heteroaryl, heteroarylC_{1-4}alkyl, heteroaryl C_{2-4} alkenyl, heterocyclic, heterocyclic C_{1-4}alkyl, and a heterocyclic C_{2-4}alkenyl moiety, which may be optionally substituted independently by halogen, nitro; halosubstituted C_{1-4}

alkyl, C_{1-4} alkyl, amino, mono or di-C_{1-4} alkyl substituted amine, OR_a, $C(O)R_a$, $NR_aC(O)OR_a$, $OC(O)NR_6R_7$, hydroxy; $NR_9C(O)R_a$, $S(O)_mR_a$, $C(O)NR_6R_7$, C(O)OH, $C(O)OR_a$, $S(O)_2NR_6R_7$, and $NHS(O)_2R_a$;

R_4 and R_5 are independently selected from the group consisting of hydrogen, optionally substituted C_{1-4} alkyl, optionally substituted aryl, optionally substituted aryl C_{1-4}alkyl, optionally substituted heteroaryl, optionally substituted heteroaryl C_{1-4}alkyl, heterocyclic, and heterocyclicC_{1-4} alkyl; or R_4 and R_5 together with the nitrogen to which they are attached form a 5 to 7 member ring which may optionally comprise an additional heteroatom selected from O, N and S;

R_6 and R_7 are independently selected from the group consisting of hydrogen, C_{1-4} alkyl, heteroaryl, aryl, cycloalkyl, and alkyl C_{1-4} heteroalkyl; or R_6 and R_7 together form a 5 to 7 member ring which ring may optionally contain an additional heteroatom is selected from oxygen, nitrogen or sulfur, and which ring may be optionally substituted;

R_8 is hydrogen or C_{1-4} alkyl;

R_9 is hydrogen or a C_{1-4} alkyl;

R_{10} is C_{1-10} alkyl $C(O)_2R_8$;

R_{11} is selected from the group consisting of hydrogen, optionally substituted C_{1-4} alkyl, optionally substituted aryl, optionally substituted aryl C_{1-4}alkyl, optionally substituted heteroaryl, optionally substituted heteroarylC_{1-4}alkyl, optionally substituted heterocyclic, and optionally substituted heterocyclicC_{1-4}alkyl;

R_a is selected from the group consisting of alkyl, aryl, arylC_{1-4}alkyl, heteroaryl, heteroaryl C_{1-4}alkyl, heterocyclic, $COOR_a$, and a heterocyclic C_{1-4}alkyl moiety, all of which moieties may be optionally substituted;

n is an integer having a value of 0 to 5;

m is an integer having a value of 0 to 5;

o is an integer having a value of 1 to 4;

q is 0, or an integer having a value of 1 to 10;

s is an integer having a value of 1 to 3;

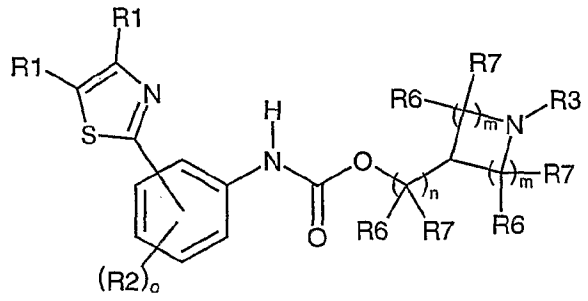
t is 0, or an integer having a value of 1 or 2; and

m' is 0, or an integer having a value of 1 or 2.

DETAILED DESCRIPTION OF THE INVENTION

This invention relates to novel thiazole aniline compounds, pharmaceutical compositions, processes for their preparation, and use thereof in treating M_3 muscarinic acetylcholine receptor mediated diseases.

In a preferred embodiment of the present invention, the compound is of formula (I) hereinbelow:



(I)

wherein:

the thiazole is ortho to the nitrogen;

R1 is selected from the group consisting of halogen, C_{1-5}alkyl, CH_2F, CHF_2;

R2 is selected from the group consisting of hydrogen, C_{1-5}alkyl, aryl, halogen, hydroxy and alkoxy;

R3 is selected from the group consisting of hydrogen, C_{1-5}alkyl, cycloalkyl, cycloalkyl C_{1-5} alkyl, C_{2-4}alkenyl, C_{2-4}alkenylaryl; cycloalkyl C_{1-5} alkyl, and C_{1-4}alkylaryl, which may be optionally substituted independently by a substituent selected from the group consisting of halogen, nitro, halosubstituted C_{1-4} alkyl, C_{1-4} alkyl, amino, mono or di-C_{1-4} alkyl substituted amine, OR_a; $C(O)R_a$, $NR_aC(O)OR_a$, $OC(O)NR_6R_7$, hydroxy, $NR_9C(O)R_a$, $S(O)_{m'}R_a$, $C(O)NR_6R_7$, C(O)OH, $C(O)OR_a$, $S(O)_2NR_6R_7$, and $NHS(O)_2R_a$;

R_6 and R_7 are selected from the group consisting of hydrogen, and C_{1-4} alkyl, or R_6 and R_7 together form a 5 to 7 member ring which ring may optionally contain an

additional heteroatom selected from oxygen, nitrogen or sulfur, and which ring may be optionally substituted;

n is 1 or 2; and independently

m is 1 or 2.

Suitably, R1 is independently selected from the group consisting of hydrogen, halogen, NR_6R_7, OH, OR_a, $C(O)R_a$, $NR_aC(O)OR_a$, $OC(O)NR_6R_7$, $NR_9C(O)R_a$, $S(O)_mR_a$, $C(O)NR_6R_7$, C(O)OH, $C(O)OR_a$, $S(O)_2NR_6R_7$, NHS(O)2Ra, C_{1-5}alkyl, aryl, C_{1-4}alkylaryl, C_{2-4}alkenyl, C_{2-4}alkenylaryl, cycloalkyl, C_{1-5} alkylcycloalkyl, heteroaryl, C_{1-4}alkylheteroaryl, C_{2-4} alkenylheteroaryl, heterocyclic, C_{1-4}alkyl heterocyclic, and a C_{2-4}alkenyl moiety heterocyclic, which when feasible may be optionally substituted independently by a substituent selected fom the group consisting of halogen, nitro, C_{1-5}alkyl, amino, mono or di-C_{1-4} alkyl substituted amine, OR_a, $C(O)R_a$, $NR_aC(O)OR_a$, $OC(O)NR_6R_7$, hydroxy, $NR_9C(O)R_a$, $S(O)_mR_a$, $C(O)NR_6R_7$, C(O)OH, $C(O)OR_a$, $S(O)_2NR_6R_7$, and $NHS(O)_2R_a$. or two R1 moieties together may form a 5 to 6 membered saturated or unsaturated ring; and wherein the alkyl, aryl, arylalkyl, heteroaryl, heteroaryl alkyl, heterocyclic, heterocyclicalkyl groups may be optionally substituted.

Suitably, R2 is selected from the group consisting of hydrogen, halogen, nitro, cyano, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy, halosubstituted C_{1-10} alkoxy, azide, $(CR_8R_8)qS(O)_tR_a$, $(CR_8R_8)qOR_a$, hydroxy, hydroxy substituted C_{1-4}alkyl, aryl, aryl C_{1-4} alkyl, aryloxy, arylC_{1-4} alkyloxy, aryl C_{2-10} alkenyl, heteroaryl, heteroarylalkyl, heteroaryl C_{1-4} alkyloxy, heteroaryl C_{2-10} alkenyl, heterocyclic, heterocyclic C_{1-4}alkyl, heterocyclicC_{2-10} alkenyl, $(CR_8R_8)qNR_4R_5$, C_{2-10} alkenyl $C(O)NR_4R_5$, $(CR_8R_8)qC(O)NR_4R_5$, $(CR_8R_8)q$ $C(O)NR_4R_{10}$, $S(O)_3R_8$, $(CR_8R_8)qC(O)R_{11}$, C_{2-10} alkenyl$C(O)R_{11}$, $(CR_8R_8)qC(O)OR_{11}$, C_{2-10}alkenyl$C(O)OR_{11}$, $(CR_8R_8)qOC(O)R_{11}$, $(CR_8R_8)qNR_4C(O)R_{11}$, $(CR_8R_8)q$ $NHS(O)_2R_{13}$, $(CR_8R_8)q$ $S(O)_2NR_4R_5$, $(CR_8R_8)qC(NR_4)NR_4R_5$, and $(CR_8R_8)q$ $NR_4C(NR_5)R_{11}$; or two R2

moieties together may form a 5 to 6 membered saturated or unsaturated ring; and wherein the alkyl, aryl, arylalkyl, heteroaryl, heteroaryl alkyl, heterocyclic, heterocyclicalkyl groups may be optionally substituted.

Suitably R3 is independently selected from the group consisting of hydrogen, C_{1-5}alkyl, aryl, C_{1-4}alkylaryl, C_{2-4}alkenyl, C_{2-4}alkenylaryl, C_{1-5} alkylcycloalkyl, cycloalkyl, cycloalkyl C_{1-5} alkyl, heteroaryl, heteroarylC_{1-4}alkyl, heteroaryl C_{2-4} alkenyl, heterocyclic, heterocyclic C_{1-4}alkyl, and a heterocyclic C_{2-4}alkenyl moiety, which may be optionally substituted independently by a substituent selected from the group consisting of halogen, nitro, halosubstituted C_{1-4} alkyl, C_{1-4} alkyl, amino, mono or di-C_{1-4} alkyl substituted amine, OR_a, $C(O)R_a$, $NR_aC(O)OR_a$, $OC(O)NR_6R_7$, hydroxy, $NR_9C(O)R_a$, $S(O)_mR_a$, $C(O)NR_6R_7$, C(O)OH, $C(O)OR_a$, $S(O)_2NR_6R_7$, and $NHS(O)_2R_a$.

Suitably, R_4 and R_5 are independently selected from the group consisting of hydrogen, optionally substituted C_{1-4} alkyl, optionally substituted aryl, optionally substituted aryl C_{1-4}alkyl, optionally substituted heteroaryl, optionally substituted heteroaryl C_{1-4}alkyl, heterocyclic, and heterocyclicC_{1-4} alkyl, or R_4 and R_5 together with the nitrogen to which they are attached form a 5 to 7 member ring which may optionally comprise an additional heteroatom selected from O, N and S.

Suitably, R_6 and R_7 are independently selected from the group consisting of hydrogen, C_{1-4} alkyl, heteroaryl, aryl, cycloalkyl, and alkyl C_{1-4} heteroalkyl; or R_6 and R_7 together form a 5 to 7 member ring which ring may optionally contain an additional heteroatom is selected from oxygen, nitrogen or sulfur, and which ring may be optionally substitued;

Suitably, R_8 is hydrogen or C_{1-4} alkyl.

Sutiably, R_9 is hydrogen or a C_{1-4} alkyl.

Sutiably, R_{10} is C_{1-10} alkyl $C(O)_2R_8$.

Suitably, R_{11} is selected from the group consisting of hydrogen, optionally substituted C_{1-4} alkyl, optionally substituted aryl, optionally substituted aryl C_{1-4}alkyl, optionally substituted heteroaryl, optionally substituted heteroarylC_{1-4}alkyl, optionally substituted heterocyclic, and optionally substituted heterocyclicC_{1-4}alkyl.

Suitably, R_a is selected from the group consisting of alkyl, aryl, arylC_{1-4}alkyl, heteroaryl, heteroaryl C_{1-4}alkyl, heterocyclic, $COOR_a$, and a heterocyclic C_{1-4}alkyl moiety, all of which moieties may be optionally substituted.

Suitably, n is an integer having a value of 0 to 5; m is an integer having a value of 0 to 5; o is an integer having a value of 1 to 4; q is 0, or an integer having a value of 1 to 10; s is an integer having a value of 1 to 3; t is 0, or an integer having a value of 1 or 2; m' is 0, or an integer having a value of 1 or 2.

All of the aryl, heteroaryl, and heterocyclic containing moieties may be optionally substituted as defined herein below.

For use herein the term "the aryl, heteroaryl, and heterocyclic containing moieties" refers to both the ring and the alkyl, or if included, the alkenyl rings, such as aryl, arylalkyl, and aryl alkenyl rings. The term "moieties" and "rings" may be interchangeably used throughout.

As used herein, "optionally substituted" unless specifically defined shall mean such groups as halogen, such as fluorine, chlorine, bromine or iodine; hydroxy; hydroxy substituted C_{1-10}alkyl; C_{1-10} alkoxy, such as methoxy or ethoxy; $S(O)_{m'}C_{1-10}$ alkyl, wherein m' is 0, 1 or 2, such as methyl thio, methyl sulfinyl or methyl sulfonyl; amino, mono & di-substituted amino, such as in the NR_4R_5 group; $NHC(O)R_4$; $C(O)NR_4R_5$; C(O)OH; $S(O)_2NR_4R_5$; $NHS(O)_2R_{20}$, C_{1-10} alkyl, such as methyl, ethyl, propyl, isopropyl, or t-butyl; halosubstituted C_{1-10} alkyl, such CF_3; an optionally substituted aryl, such as phenyl, or an optionally substituted arylalkyl, such as benzyl or phenethyl, optionally substituted heterocylic, optionally substituted heterocyclicalkyl, optionally substituted heteroaryl, optionally substituted heteroaryl

alkyl, wherein these aryl , heteroaryl, or heterocyclic moieties may be substituted one to two times by halogen; hydroxy; hydroxy substituted alkyl; C_{1-10} alkoxy; $S(O)_mC_{1-10}$ alkyl; amino, mono & di-substituted alkyl amino, such as in the NR_4R_5 group; C_{1-10} alkyl, or halosubstituted C_{1-10} alkyl, such as CF_3.

Suitable pharmaceutically acceptable salts are well known to those skilled in the art and include basic salts of inorganic and organic acids, such as hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methane sulphonic acid, ethane sulphonic acid, acetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid and mandelic acid. In addition, pharmaceutically acceptable salts of compounds of Formula (I) may also be formed with a pharmaceutically acceptable cation. Suitable pharmaceutically acceptable cations are well known to those skilled in the art and include alkaline, alkaline earth, ammonium and quaternary ammonium cations.

The following terms, as used herein, refer to:

- "halo" - all halogens, that is chloro, fluoro, bromo and iodo.
- "C_{1-10}alkyl" or "alkyl" - both straight and branched chain moieties of 1 to 10 carbon atoms, unless the chain length is otherwise limited, including, but not limited to, methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *iso*-butyl, *tert*-butyl, *n*-pentyl and the like.
- "cycloalkyl" is used herein to mean cyclic moiety, preferably of 3 to 8 carbons, including but not limited to cyclopropyl, cyclopentyl, cyclohexyl, and the like.
- "alkenyl" is used herein at all occurrences to mean straight or branched chain moiety of 2-10 carbon atoms, unless the chain length is limited thereto, including, but not limited to ethenyl, 1-propenyl, 2-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl and the like.
- "aryl" - phenyl and naphthyl;
- "heteroaryl" (on its own or in any combination, such as "heteroaryloxy", or "heteroaryl alkyl") - a 5-10 membered aromatic ring system in which one or more rings contain one or more heteroatoms selected from the group consisting of N, O or S, such as, but not limited, to pyrrole, pyrazole, furan, thiophene, quinoline, isoquinoline, quinazolinyl, pyridine, pyrimidine, oxazole, tetrazole, thiazole, thiadiazole, triazole, imidazole, or benzimidazole.

• "heterocyclic" (on its own or in any combination, such as "heterocyclicalkyl") - a saturated or partially unsaturated 4-10 membered ring system in which one or more rings contain one or more heteroatoms selected from the group consisting of N, O, or S; such as, but not limited to, pyrrolidine, piperidine, piperazine, morpholine, tetrahydropyran, thiomorpholine, or imidazolidine. Furthermore, sulfur may be optionally oxidized to the sulfone or the sulfoxide.

• "arylalkyl" or "heteroarylalkyl" or "heterocyclicalkyl" is used herein to mean C_{1-10} alkyl, as defined above, attached to an aryl, heteroaryl or heterocyclic moiety, as also defined herein, unless otherwise indicated.

• "sulfinyl" - the oxide S (O) of the corresponding sulfide, the term "thio" refers to the sulfide, and the term "sulfonyl" refers to the fully oxidized $S(O)_2$ moiety.

• "wherein two R_1 moieties (or two Y moieties) may together form a 5 or 6 membered saturated or unsaturated ring" is used herein to mean the formation of an aromatic ring system, such as naphthalene, or is a phenyl moiety having attached a 6 membered partially saturated or unsaturated ring such as a C_6 cycloalkenyl, i.e. hexene, or a C_5 cycloalkenyl moiety, such as cyclopentene.

Illustrative compounds of Formula (I) include:

[2-(4-Methyl-thiazol-2-yl)-phenyl]-carbamic acid piperidin-4-ylmethyl ester

[2-(4-Ethyl-thiazol-2-yl)-phenyl]-carbamic acid piperidin-4-ylmethyl ester

{2-[4-(1,1-Difluoro-methyl)-thiazol-2-yl]-phenyl}-carbamic acid piperidin-4-ylmethyl ester

(2-Thiazol-2-yl-phenyl)-carbamic acid piperidin-4-ylmethyl ester; compound with 2,2,2-trifluoro-acetic acid

[2-(4-Propyl-thiazol-2-yl)-phenyl]-carbamic acid piperidin-4-ylmethyl ester

[2-(4-Methyl-thiazol-2-yl)-phenyl]-carbamic acid (2R,6R)-2,6-dimethyl-piperidin-4-ylmethyl ester

[2-(4-Isopropyl-thiazol-2-yl)-phenyl]-carbamic acid piperidin-4-ylmethyl ester

[2-(4-tert-Butyl-thiazol-2-yl)-phenyl]-carbamic acid piperidin-4-ylmethyl ester

[2-(4-Bromo-thiazol-2-yl)-phenyl]-carbamic acid piperidin-4-ylmethyl ester

[2-(4-Chloro-thiazol-2-yl)-phenyl]-carbamic acid piperidin-4-ylmethyl ester

[2-(4-Isobutyl-thiazol-2-yl)-phenyl]-carbamic acid piperidin-4-ylmethyl ester

[2-(4-Cyclopropylmethyl-thiazol-2-yl)-phenyl]-carbamic acid piperidin-4-ylmethyl ester

[2-(4-Cyclopropyl-thiazol-2-yl)-phenyl]-carbamic acid piperidin-4-ylmethyl ester

[2-(4-Cyclobutyl-thiazol-2-yl)-phenyl]-carbamic acid piperidin-4-ylmethyl ester

[2-(4-Trifluoromethyl-thiazol-2-yl)-phenyl]-carbamic acid piperidin-4-ylmethyl ester

[2-(4-Fluoromethyl-thiazol-2-yl)-phenyl]-carbamic acid piperidin-4-ylmethyl ester

{2-[4-(1,1-Difluoro-ethyl)-thiazol-2-yl]-phenyl}-carbamic acid piperidin-4-ylmethyl ester

{2-[4-(2-Fluoro-ethyl)-thiazol-2-yl]-phenyl}-carbamic acid piperidin-4-ylmethyl ester

{2-[4-(2,2-Difluoro-ethyl)-thiazol-2-yl]-phenyl}-carbamic acid piperidin-4-ylmethyl ester

[2-(4-Methoxymethyl-thiazol-2-yl)-phenyl]-carbamic acid piperidin-4-ylmethyl ester

[2-(4-Hydroxymethyl-thiazol-2-yl)-phenyl]-carbamic acid piperidin-4-ylmethyl ester

{2-[4-(1-Hydroxy-ethyl)-thiazol-2-yl]-phenyl}-carbamic acid piperidin-4-ylmethyl ester

{2-[4-((R)-1-Hydroxy-ethyl)-thiazol-2-yl]-phenyl}-carbamic acid piperidin-4-ylmethyl ester

{2-[4-(2-Hydroxy-ethyl)-thiazol-2-yl]-phenyl}-carbamic acid piperidin-4-ylmethyl ester

[2-(4-Amino-thiazol-2-yl)-phenyl]-carbamic acid piperidin-4-ylmethyl ester

[5-Fluoro-2-(4-methyl-thiazol-2-yl)-phenyl]-carbamic acid piperidin-4-ylmethyl ester

[2-(4-Ethyl-thiazol-2-yl)-4-hydroxy-phenyl]-carbamic acid piperidin-4-ylmethyl ester

[2-(4-Methyl-thiazol-2-yl)-phenyl]-carbamic acid (2R,6S)-2,6-dimethyl-piperidin-4-ylmethyl ester

[2-(4-Methyl-thiazol-2-yl)-phenyl]-carbamic acid (2R,6S)-2,6-dimethyl-piperidin-4-ylmethyl ester

[2-(4-Methyl-thiazol-2-yl)-phenyl]-carbamic acid (2R,6S)-1-benzyl-2,6-dimethyl-piperidin-4-ylmethyl ester

[2-(4-Methyl-thiazol-2-yl)-phenyl]-carbamic acid (2R,6S)-1-benzyl-2,6-dimethyl-piperidin-4-ylmethyl ester

[2-(4-Methyl-thiazol-2-yl)-phenyl]-carbamic acid (2R,6R)-2,6-dimethyl-piperidin-4-ylmethyl ester

[2-(4-Methyl-thiazol-2-yl)-phenyl]-carbamic acid (2R,6R)-2,6-dimethyl-piperidin-4-ylmethyl ester

[2-(4-Methyl-thiazol-2-yl)-phenyl]-carbamic acid (2R,6R)-1-benzyl-2,6-dimethyl-piperidin-4-ylmethyl ester

[2-(4-Methyl-thiazol-2-yl)-phenyl]-carbamic acid 4-fluoro-piperidin-4-ylmethyl ester

[2-(4-Methyl-thiazol-2-yl)-phenyl]-carbamic acid 1-butyl-piperidin-4-ylmethyl ester

[2-(4-Methyl-5-methylcarbamoyl-thiazol-2-yl)-phenyl]-carbamic acid piperidin-4-ylmethyl ester

[2-(5-Methyl-thiazol-2-yl)-phenyl]-carbamic acid piperidin-4-ylmethyl ester

[2-(4,5-Dimethyl-thiazol-2-yl)-phenyl]-carbamic acid piperidin-4-ylmethyl ester

[2-(4-Acetyl-thiazol-2-yl)-phenyl]-carbamic acid piperidin-4-ylmethyl ester

{2-[4-(2-Benzyloxy-ethyl)-thiazol-2-yl]-phenyl}-carbamic acid piperidin-4-ylmethyl ester

[2-(4-Methylcarbamoyl-thiazol-2-yl)-phenyl]-carbamic acid piperidin-4-ylmethyl ester

2-[2-(Piperidin-4-ylmethoxycarbonylamino)-phenyl]-thiazole-4-carboxylic acid ethyl ester

[2-(4-Dimethylaminomethyl-thiazol-2-yl)-phenyl]-carbamic acid piperidin-4-ylmethyl ester

[2-(4-Phenyl-thiazol-2-yl)-phenyl]-carbamic acid piperidin-4-ylmethyl ester

[2-(4-Thiophen-3-yl-thiazol-2-yl)-phenyl]-carbamic acid piperidin-4-ylmethyl ester

[2-(4-Ethyl-thiazol-2-yl)-4-fluoro-phenyl]-carbamic acid piperidin-4-ylmethyl ester

tert-Butyl 4-{[({[4-(4,4,5,5-tetrametyl-[1,3,2]dioxaborolan-2-yl) phenyl]amino}carbonyl)oxy]methyl}piperidine-1-carboxylate

tert-Butyl 4-{[({[3-(4,4,5,5-tetrametyl-[1,3,2]dioxaborolan-2-yl) phenyl]amino}carbonyl)oxy]methyl}piperidine-1-carboxylate

tert-Butyl 4-{[({[4-(4-chloro-1,3-thiazol-2-yl) phenyl]amino}carbonyl)oxy]methyl}piperidine-1-carboxylate

tert-Butyl 4-{[({[3-(4-chloro-1,3-thiazol-2-yl) phenyl]amino}carbonyl)oxy]methyl}piperidine-1-carboxylate

Piperidin-4-ylmethyl 4-(4-chloro-1,3-thiazol-2-yl)phenylcarbamate hydrochloride

Piperidin-4-ylmethyl 3-(4-chloro-1,3-thiazol-2-yl)phenylcarbamate hydrochloride

1-cyclohexylmethyl-piperidin-4-ylmethyl 4-(4-chloro-1,3-thiazol-2-yl)phenylcarbamate

1-cyclohexylmethyl-piperidin-4-ylmethyl 3-(4-chloro-1,3-thiazol-2-yl)phenylcarbamate
4-[4-(4-Chloro-thiazol-2-yl)-phenylcarbamoyloxymethyl]-1-cyclohexylmethyl-1-methyl-piperidinium iodide
4-[3-(4-Chloro-thiazol-2-yl)-phenylcarbamoyloxymethyl]-1-cyclohexylmethyl-1-methyl-piperidinium iodide
4-[4-(4-Chloro-thiazol-2-yl)-phenylcarbamoyloxymethyl]-1,1-dimethyl-piperidinium; and
4-[3-(4-Chloro-thiazol-2-yl)-phenylcarbamoyloxymethyl]-1,1-dimethyl-piperidinium; or a pharmaceutically acceptable salt thereof.

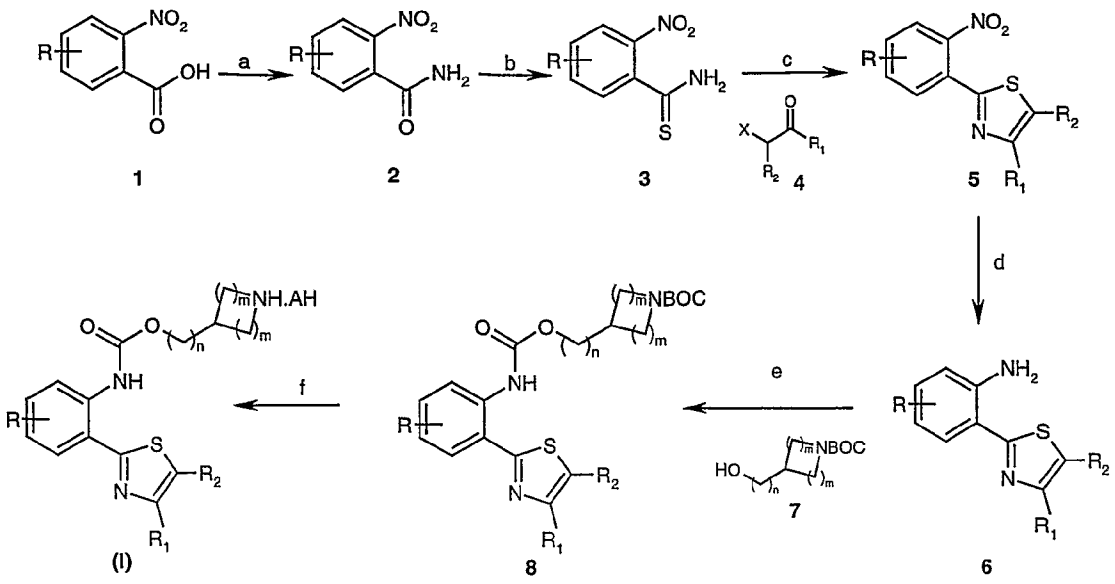
Preferred compounds useful in the present invention include
[2-(4-Bromo-thiazol-2-yl)-phenyl]-carbamic acid piperidin-4-ylmethyl ester
[2-(4-Chloro-thiazol-2-yl)-phenyl]-carbamic acid piperidin-4-ylmethyl ester
[2-(4-Methyl-thiazol-2-yl)-phenyl]-carbamic acid piperidin-4-ylmethyl ester
{2-[4-(1,1-Difluoro-methyl)-thiazol-2-yl]-phenyl}-carbamic acid piperidin-4-ylmethyl ester
[2-(4-Fluoromethyl-thiazol-2-yl)-phenyl]-carbamic acid piperidin-4-ylmethyl ester.
Also preferred compounds useful in the present invention include:
[2-(4-Ethyl-thiazol-2-yl)-phenyl]-carbamic acid piperidin-4-ylmethyl ester
(2-Thiazol-2-yl-phenyl)-carbamic acid piperidin-4-ylmethyl ester; compound with 2,2,2-trifluoro-acetic acid
[2-(4-Propyl-thiazol-2-yl)-phenyl]-carbamic acid piperidin-4-ylmethyl ester
[2-(4-Methyl-thiazol-2-yl)-phenyl]-carbamic acid (2R,6R)-2,6-dimethyl-piperidin-4-ylmethyl ester
[2-(4-Isopropyl-thiazol-2-yl)-phenyl]-carbamic acid piperidin-4-ylmethyl ester
[2-(4-tert-Butyl-thiazol-2-yl)-phenyl]-carbamic acid piperidin-4-ylmethyl ester
[2-(4-Bromo-thiazol-2-yl)-phenyl]-carbamic acid piperidin-4-ylmethyl ester
[2-(4-Chloro-thiazol-2-yl)-phenyl]-carbamic acid piperidin-4-ylmethyl ester
[2-(4-Isobutyl-thiazol-2-yl)-phenyl]-carbamic acid piperidin-4-ylmethyl ester
[2-(4-Cyclopropylmethyl-thiazol-2-yl)-phenyl]-carbamic acid piperidin-4-ylmethyl ester
[2-(4-Cyclopropyl-thiazol-2-yl)-phenyl]-carbamic acid piperidin-4-ylmethyl ester
[2-(4-Cyclobutyl-thiazol-2-yl)-phenyl]-carbamic acid piperidin-4-ylmethyl ester

[2-(4-Trifluoromethyl-thiazol-2-yl)-phenyl]-carbamic acid piperidin-4-ylmethyl ester
{2-[4-(1,1-Difluoro-ethyl)-thiazol-2-yl]-phenyl}-carbamic acid piperidin-4-ylmethyl ester
{2-[4-(2-Fluoro-ethyl)-thiazol-2-yl]-phenyl}-carbamic acid piperidin-4-ylmethyl ester
{2-[4-(2,2-Difluoro-ethyl)-thiazol-2-yl]-phenyl}-carbamic acid piperidin-4-ylmethyl ester
[2-(4-Methoxymethyl-thiazol-2-yl)-phenyl]-carbamic acid piperidin-4-ylmethyl ester
[2-(4-Hydroxymethyl-thiazol-2-yl)-phenyl]-carbamic acid piperidin-4-ylmethyl ester
{2-[4-(1-Hydroxy-ethyl)-thiazol-2-yl]-phenyl}-carbamic acid piperidin-4-ylmethyl ester
{2-[4-((R)-1-Hydroxy-ethyl)-thiazol-2-yl]-phenyl}-carbamic acid piperidin-4-ylmethyl ester
{2-[4-(2-Hydroxy-ethyl)-thiazol-2-yl]-phenyl}-carbamic acid piperidin-4-ylmethyl ester
[2-(4-Amino-thiazol-2-yl)-phenyl]-carbamic acid piperidin-4-ylmethyl ester
[5-Fluoro-2-(4-methyl-thiazol-2-yl)-phenyl]-carbamic acid piperidin-4-ylmethyl ester
[2-(4-Ethyl-thiazol-2-yl)-4-hydroxy-phenyl]-carbamic acid piperidin-4-ylmethyl ester
[2-(4-Methyl-thiazol-2-yl)-phenyl]-carbamic acid (2R,6S)-2,6-dimethyl-piperidin-4-ylmethyl ester
[2-(4-Methyl-thiazol-2-yl)-phenyl]-carbamic acid (2R,6S)-2,6-dimethyl-piperidin-4-ylmethyl ester
[2-(4-Methyl-thiazol-2-yl)-phenyl]-carbamic acid (2R,6S)-1-benzyl-2,6-dimethyl-piperidin-4-ylmethyl ester
[2-(4-Methyl-thiazol-2-yl)-phenyl]-carbamic acid (2R,6S)-1-benzyl-2,6-dimethyl-piperidin-4-ylmethyl ester
[2-(4-Methyl-thiazol-2-yl)-phenyl]-carbamic acid (2R,6R)-2,6-dimethyl-piperidin-4-ylmethyl ester
[2-(4-Methyl-thiazol-2-yl)-phenyl]-carbamic acid (2R,6R)-2,6-dimethyl-piperidin-4-ylmethyl ester
[2-(4-Methyl-thiazol-2-yl)-phenyl]-carbamic acid (2R,6R)-1-benzyl-2,6-dimethyl-piperidin-4-ylmethyl ester
[2-(4-Methyl-thiazol-2-yl)-phenyl]-carbamic acid 4-fluoro-piperidin-4-ylmethyl ester

[2-(4-Methyl-thiazol-2-yl)-phenyl]-carbamic acid 1-butyl-piperidin-4-ylmethyl ester
[2-(4-Methyl-5-methylcarbamoyl-thiazol-2-yl)-phenyl]-carbamic acid piperidin-4-ylmethyl ester
[2-(5-Methyl-thiazol-2-yl)-phenyl]-carbamic acid piperidin-4-ylmethyl ester
[2-(4,5-Dimethyl-thiazol-2-yl)-phenyl]-carbamic acid piperidin-4-ylmethyl ester
[2-(4-Acetyl-thiazol-2-yl)-phenyl]-carbamic acid piperidin-4-ylmethyl ester
{2-[4-(2-Benzyloxy-ethyl)-thiazol-2-yl]-phenyl}-carbamic acid piperidin-4-ylmethyl ester
[2-(4-Methylcarbamoyl-thiazol-2-yl)-phenyl]-carbamic acid piperidin-4-ylmethyl ester
2-[2-(Piperidin-4-ylmethoxycarbonylamino)-phenyl]-thiazole-4-carboxylic acid ethyl ester
[2-(4-Dimethylaminomethyl-thiazol-2-yl)-phenyl]-carbamic acid piperidin-4-ylmethyl ester
[2-(4-Phenyl-thiazol-2-yl)-phenyl]-carbamic acid piperidin-4-ylmethyl ester
[2-(4-Thiophen-3-yl-thiazol-2-yl)-phenyl]-carbamic acid piperidin-4-ylmethyl ester; and
[2-(4-Ethyl-thiazol-2-yl)-4-fluoro-phenyl]-carbamic acid piperidin-4-ylmethyl ester.

Methods of Preparation.

The compounds of Formula (I) may be obtained by applying synthetic procedures, some of which are illustrated in the Schemes below. The synthesis provided for these Schemes is applicable for producing compounds of Formula (I) having a variety of different R, R1 which are reacted, employing substituents which are suitable protected, to achieve compatibility with the reactions outlined herein. Subsequent deprotection, in those cases, then affords compounds of the nature generally disclosed. Once the thiazole nucleus has been established, further compounds of these Formulas may be prepared by applying techniques for functional groups interconversion, well known in the art. While the Schemes are shown with compounds only of Formula (I), this is merely for illustration purpose only.



Reagents and conditions: a) CDI, NH3, MeOH; b) Lawesson's reagent, toluene, reflux; c) reflux, ethanol; d) H2, Pd/C MeOH

e) Triphosgene, DIPEA, 7; f) Trifluoroacetic aicd

Scheme 1

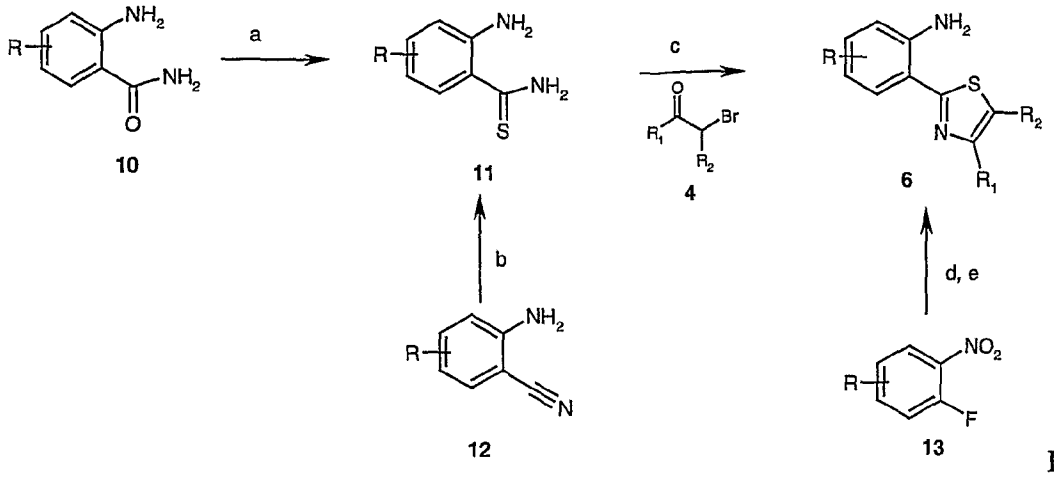
The desired compounds of formula (I) can be prepared as outlined in Scheme 1. The carbamides **2** can be prepared from the corresponding carboxylic acids **1** using standard methods well known in the art such as carbodiimidazole (CDI) in methanolic ammonia. The aryl thioamides **3** can be prepared from the corresponding carbamides **2** using standard reagents well known in the art such as the commercially available Lawesson's reagent. Reacting thioamide **3** with the appropriate α-halomethylketone **4** in an organic solvent such as ethanol gives the nitro-aryl thiazole **5**. The anilines **6** can be prepared from the corresponding nitro-aryl thiazole **5** using standard reduction methods well known in the art such as catalytic hydrogenation. Reacting sequentially the suitably protected aminoalcohol **7** with triphosgene in an organic solvent such as THF, then with the aniline **6** gives the carbamate derivative **8**. Removal of the protecting group using standard conditions such as treatment with trifluoroacetic acid in dichloromethane gives the target compound of formula (I).

If the required α-halomethylketone **4** is not commercially available, it can be prepared as outlined in Scheme 2. The commercially available methylketone **9** can be converted to the α-bromomethylketone **4** using standard conditions well known in the art such as bromine in a suitable organic solvent such as methanol.

Reagents and conditions: Br_2, MeOH

Scheme 2

Alternatively, the anilines **6** can be prepared as outlined in Scheme 3. The ortho-substituted carbamide aniline **10** can be converted to the corresponding thioamide **11** by reacting with the Lawesson's reagent at reflux in an organic solvent such as toluene. Reacting the thioamide **11** with the α-halomethylketone **4** in a suitable organic solvent such as ethanol gives the aniline-thiazole derivative **6**. The thioamide **11** can also be prepared by reacting the ortho-cyanoaniline **12** with gaseous hydrogen sulfide according to known literature procedures (J. Heterocyl. Chem **1974**, *11(5)*, 747-750). The anilines **6** may also be prepared by reacting ortho nitrofluorobenzenes **13** with 2-lithiated thiazole derivatives followed by reduction of the nitro moiety using standard conditions well known in the art such as catlytic hydrogenation in a suitable organic solvent such as ethanol.

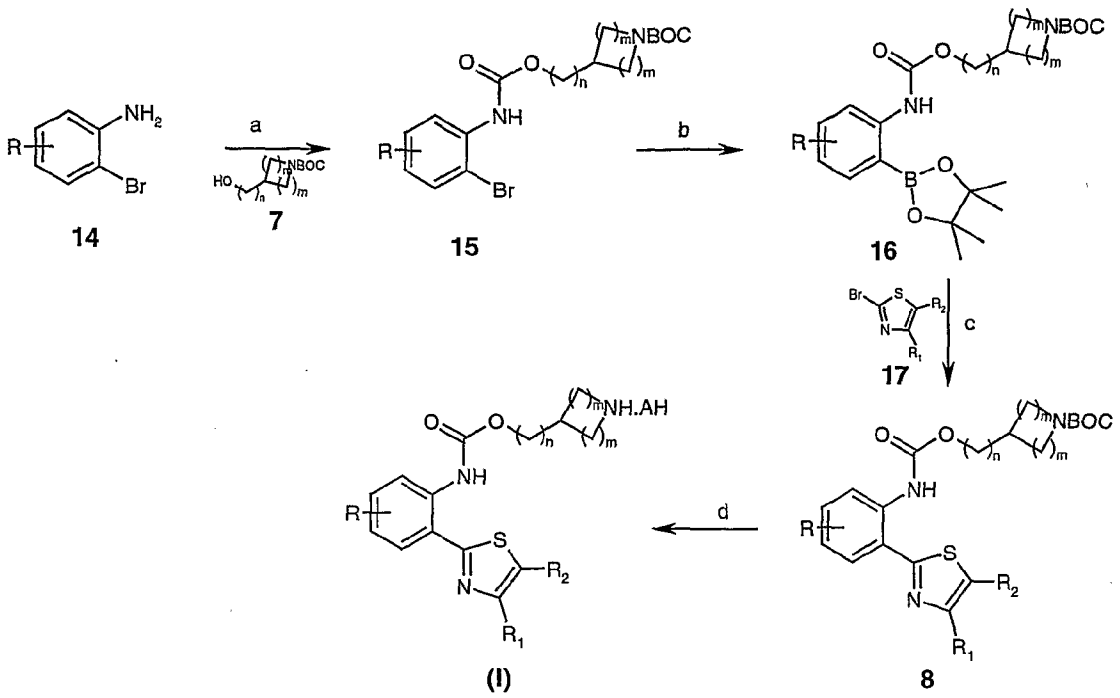


Re

agents and conditions:a) Lawesson's reagent, toluene reflux; b) H2S; c) Ethanol, reflux; d) 4-substituted-thiazole, nBuLi; e) H2, Pd/C

Scheme 3

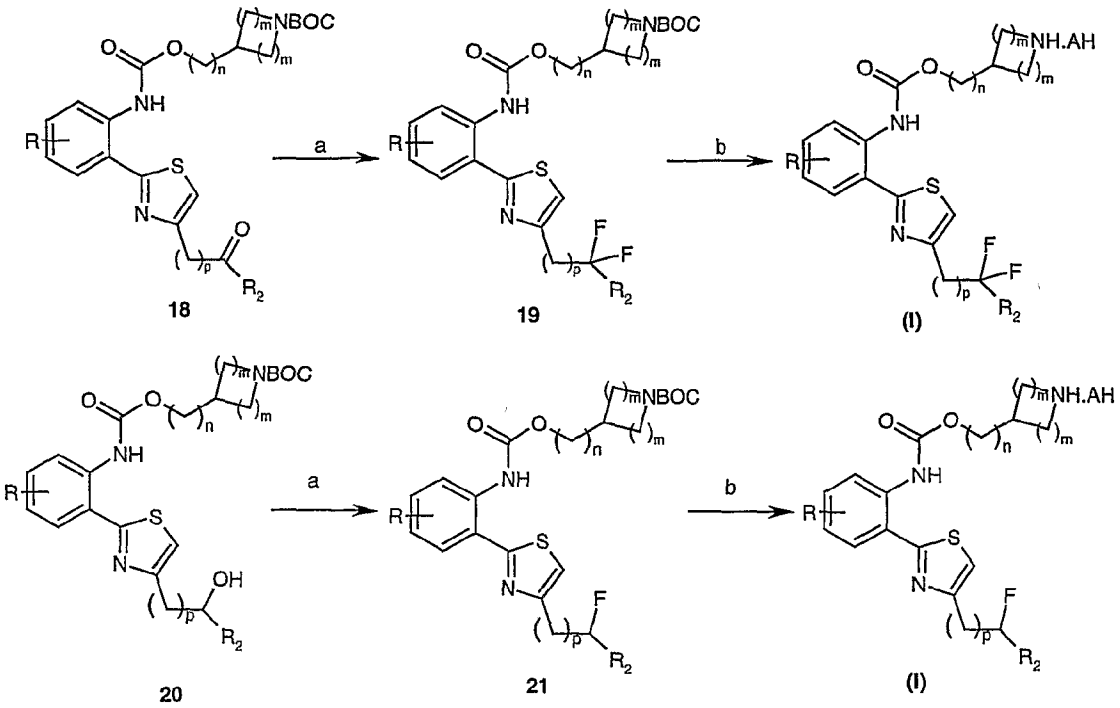
The desired compounds of formula (I) can also be prepared as outlined in Scheme 4. Reacting sequentially the suitably protected aminoalcohol **7** with triphosgene in an organic solvent such as THF, then with the bromoaniline **14** gives the carbamate derivative **15**. Reacting with bis(pinacolato)diboron in the presence of catalytic amounts of palladium(II) chloride following literaure procedure (J. Org. Chem. **2000**, *65*, 9268-9271) gives the boronate ester **16**. The palladium(0) mediated coupling of the boronate ester **16** with the 2-bromothiazole derivative **17** gives the carbamate derivative **8**. Removal of the protecting group using standard conditions such as treatment with trifluoroacetic acid in dichloromethane gives the target compound of formula (I).



Reagents and conditions: a) Triphosgene, DIPEA, 7; b) PdCl2(dppf), KOAc, DME, bis(pinacolato) diboron c) 17, Pd(PPh3)4, DME, NEt3, water; e) trifluoroacetic acid

Scheme 4

The desired compounds of formula (I) can also be prepared by functionalisation of advance intermediates as outlined in Scheme 5. Reacting the ketone or aldehyde **18** or the alcohol **20** with a fluorinating agent such as diethylaminosulfurtrifluoride (DAST) in an organic solvent such as DCM gives the corresponding difluoro derivative **19** or monofluoro derivative **20**. Removal of the protecting group on **19** or **20** using standard conditions such as treatment with trifluoroacetic acid in dichloromethane gives the target compounds of formula (I).



Reagents and conditions: a) DAST, DCM; b) trifluoroacetic acid

Scheme 5

SYNTHETIC EXAMPLES

The invention will now be described by reference to the following Examples which are merely illustrative and are not to be construed as a limitation of the scope of the present invention. All temperatures are given in °C. Thin layer chromatography (t.l.c.) was carried out on silica, and column chromatography on silica (Flash column chromatography using Merck 9385 unless stated otherwise). LC/MS was conducted under the following conditions:

Column: 3.3cm x 4.6mm ID, 3um ABZ+PLUS

Flow Rate: 3ml/min

Injection Volume: 5µl

Temp: RT

Solvents: A: 0.1% Formic Acid + 10mMolar Ammonium Acetate.

B: 95% Acetonitrile + 0.05% Formic Acid

Gradient:

Time	A%	B%

0.00	100	0
0.70	100	0
4.20	0	100
5.30	0	100
5.50	100	0

GC was conducted under the following conditions:

Chemical Ionisation
Instrument HP5973MSD
Column as above
Gradient 80 to 320 at 50 degrees per min.
Gas flow 50 ml min
Run time 10 mins
Chemical ionisation collision gas- Ammonia.(Chemical Ionisation
Instrument HP5973MSD
Column 30mx0.25mm HP5
Gradient 80 to 320 at 50 degrees per min.
Gas flow 50 ml min
Run time 10 mins
Chemical ionisation collision gas- Ammonia (except where stated)

^{1}H-NMR (hereinafter "NMR") spectra were recorded at 400 MHz using a Bruker DPX 400 spectrometer. Multiplicities indicated are: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet and br indicates a broad signal. Sat. indicates a saturated solution, eq indicates the proportion of a molar equivalent of reagent relative to the principal reactant.

Intermediate 1

2-Aminobenzenecarbothioamide

Hydrogen sulphide gas (18g) was bubbled through a solution of 2-aminobenzonitrile (31.48g) and triethylamine (32ml) in pyridine (160ml) for 75mins. The mixture was

stirred for 18h and the solvent evaporated. The residue was triturated under cyclohexane (300ml) and filtered to give the title compound as a yellow solid (37.95g) NMR (d^6-DMSO 400MHz; δ) 9.75 (1H, br s, NH) 9.32 (1H, br s, NH) 7.15 (1H, dd, CH) 7.05 (1H, ddd, CH) 6.70 (1H, dd, CH) 6.52 (1H, ddd, CH) 6.16 (2H, br s, NH_2)

Intermediate 2

2-(4-methyl-1,3-thiazol-2-yl)aniline

Chloroacetone (1.3ml) was added to a solution of 2-aminobenzenecarbothioamide (2.0g) in ethanol (100ml) and the solution heated under reflux for 18h. The solvent was evaporated and the residue partitioned between dichloromethane (3x50ml) and Saturated sodium bicarbonate solution (50ml). The combined organic extracts were dried ($MgSO_4$) and the solvent evaporated. The residue was purified by chromatography on silica. Elution with 15% dichloromethane in cyclohexane gave the title compound as a dark red solid (0.86g)

LC/MS ESI R_T 3.37mins MH^+ 191.

2-(4-methyl-1,3-thiazol-2-yl)aniline (alternative route)

n-Butyl lithium (1.6M in hexanes; 31.5ml) was added dropwise to a solution of 4-methyl thiazole (5g) in dry THF (50ml) at -78oC under nitrogen over 15 mins. and stirred at -78°C for 1.5h. 2-nitrofluorobenzene (7.5g) in THF (10ml) was added over 10mins and the mixture stirred at -78°C for 0.5h then allowed to warm to room temperature and stirred for 2h. The mixture was partitioned between water and ethyl acetate and the organic phase separated, washed with brine and dried ($MgSO_4$) and evaporated. The crude material was chromatographed on silica. Elution with cyclohexane / ethyl acetate 10:1 gave an orange-brown oil. The crude material (1.28g) in ethanol (60ml) and water (20ml) containing HCl in dioxan (4M; 1.75ml) was hydrogenated over palladium catalyst (10% on carbon; 0.5g) overnight. The catalyst was filtered off and the solvent evaporated. The residue was partitioned between saturated sodium bicarbonate and ethyl acetate. The organic phase was washed with brine and dried ($MgSO_4$). The solvent was evaporated to give a brown oil which was purified by chromatography on silica (Merck 7734). Elution with cyclohexane / ethyl acetate 2:1 gave the title compound as a yellow solid (0.54g)

MS MH^+ 191 (Thermospray)

Intermediate 3

2-[4-(trifluoromethyl)-1,3-thiazol-2-yl]aniline

3-Bromo-1,1,1-trifluoroacetone (0.98ml) was added to a solution of 2-aminobenzenecarbothioamide (1.2g) in ethanol (50ml) and the mixture heated at 70°C for 22h. The sovent was evaporated and the residue purified by chromatography on silica. Elution with cyclohexane / dichloromethane 1:1 gave the title compound as a yellow solid (0.98g)

MS MH^+ 245 (Thermospray).

NMR ($CDCl_3$ 400MHz; δ) 7.63 (1H, s, CH) 7.61 (1H, dd, CH) 7.22 (1H, ddd, CH) 6.77 (1H, dd, CH) 6.72 (1H, ddd, CH) 6.03 (2H, br s, NH_2)

Intermediate 4

2-(4-cyclopropyl-1,3-thiazol-2-yl)aniline

Bromomethyl cyclopropyl ketone (CAS 69276-75-0; 3.09g) was added to a solution of 2-aminobenzenecarbothioamide (2.2g) in ethanol (50ml) and the mixture heated at 70oc for 22h. The solvent was evaporated and the residue purified by chromatography on silica. Elution with cyclohexane / dichloromethane 3:1 to methanol (5%) in dichloromethane gave the title compound as a cream coloured solid (1.17g)

NMR ($CDCl_3$ 400MHz; δ) 7.59 (1H, dd, aromatic CH) 7.14 (1H, ddd, aromatic CH) 6.725 (1H, s, aromatic CH) 6.68 (2H, m, aromatic 2xCH) 6.08 (2H, br s, NH_2) 2.07 (1H, m, CH) 0.94 (4H, m, $2xCH_2$)

Intermediate 5

2-(4-phenyl-1,3-thiazol-2-yl)aniline

2-Bromoacetophenone (CAS 70-11-1; 239mg) was added to a solution of 2-aminophenylthioamide (152mg) in ethanol (10ml). The solution was heated at 80°C under nitrogen for 6hr, cooled to room temperature and the solid filtered. The solid was partitioned between sodium bicarbonate (8%) and chloroform. The organic phase was separated and dried over $MgSO_4$. Evaporation of solvent gave the title compound as lemon solid (128mg).

LC/MS ESI R_T 3.88mins MH^+253

Intermediate 6

2-(4-thien-3-yl-1,3-thiazol-2-yl)aniline

1-Bromoaceto-3-thiophene (CAS 1468-82-2; 205mg) was added to a solution of 2-aminophenylthio~ amide (152mg) in dimethylformamide (10ml). The solution was heated at 80°C under nitrogen for 16hr. The solvent was evaporated and the residue partitioned between sodium bicarbonate (8%) and dichloromethane. The organic phase was separated and purified by chromatography (Varian Mega Bond Elut®, Si, 5g). Elution with cyclohexane / dichloromethane (2:1) gave the title compound as a beige solid (100mg).

LC/MS ESI R_T 3.81mins MH^+259

Intermediate 7

2-(4-tert-butyl-1,3-thiazol-2-yl)aniline

1-Bromo-3,3-dimethyl-2-butanone (CAS 5469-26-1; 179mg) was added to a solution of 2-aminophenyl thioamide (152mg) in dimethylformamide (10ml). The solution was heated at 80°C under nitrogen for 16hr. The solvent was evaporated and the residue partitioned between sodium bicarbonate (8%) and dichloromethane. The organic phase was separated and purified by chromatography (Varian Mega Bond Elut® Si, 5g). Elution with cyclohexane / dichloromethane (2:1) gave the title compound as a yellow oil (175mg).

LC/MS ESI R_T 3.86mins MH^+233

Intermediate 8

2-(4,5-dimethyl-1,3-thiazol-2-yl)aniline

3-Bromo-2-butanone (CAS 814-75-5; 151mg) was added to a solution of 2-aminophenylthioamide (152mg) in dimethylformamide (10ml). The solution was heated at 80°C under nitrogen for 16hr. The solvent was evaporated and the residue partitioned between sodium bicarbonate (8%) and dichloromethane. The organic phase was separated and purified by chromatography (Varian Mega Bond Elut®, Si, 5g).

Elution with cyclohexane / dichloromethane (2:1) gave the title compound as a yellow solid (74mg).

LC/MS ESI R_T 3.59mins MH^+=205

Intermediate 9

2-(4-ethyl-1,3-thiazol-2-yl)aniline

1-Bromo-2-butanone (CAS 816-40-0; 180mg) was added to a solution of 2-aminophenylthioamide (152mg) in dimethylformamide (10ml). The solution was heated at 80°C under nitrogen for 3hr. The mixture was quenched with 5% diethylamine in ethanol at 50°C for 2hr, cooled to room temperature, sodium bicarbonate solution (8%) added and extracted with dichloromethane. The organic phase was separated, diluted with cyclohexane (1:3) and purified by chromatography (Varian Mega Bond Elut®, Si, 5g). Elution with cyclohexane / dichloromethane (stepped gradient) gave the title compound as a yellow oil (150mg).

LC/MS ESI R_T 3.44mins (not ionised well)

Intermediate 10

2-(5-methyl-1,3-thiazol-2-yl)aniline

2-Bromo-propanal (CAS 19967-57-8; 165mg) was added to a solution of 2-aminophenylthioamide (152mg) in dry ether (10ml). Triethylamine (200ul) was added and the mixture heated at 80°C under nitrogen for 6hr. Water was added, and the mixture extracted with dichloromethane. The organic phase was separated, dried over $MgSO_4$, filtered and evaporated down. The residue was purified by chromatography (Biotage Flash 40i™, silica) and elution with ethyl acetate (1:10 then 3:10) gave the uncyclised material. The residue was dissolved in concentrated HCl (4ml) and heated at 60°C for 3hr, cooled to room temperature and basified with sodium bicarbonate solution (8%). The product was extracted into dichloromethane, dried over MgSO4, filtered and the solvent evaporated. The residue was purified by Varian Mega Bond Elut®, Si, 5g), elution with cyclohexane/ dichloromethane (1:1) gave the title compound as a yellow oil (66mg).

LC/MS ESI R_T 3.37mins (not ionised well)

MS Thermospray MH^+=191

Intermediate 11

2-(4-isopropyl-1,3-thiazol-2-yl)aniline

1-Bromo-3-methyl-2-butanone (CAS 19967-55-6; 164mg) was added to a solution of 2-aminophenyl thioamide (152mg) in ethanol (10ml). The solution was heated at 80°C under nitrogen for 5hr. The solvent was evaporated and the residue dissolved in DCM, washed with sodium bicarbonate solution (8%), semi-saturated brine solution, and dried over $MgSO_4$. The mixture was filtered, the solvent eavaporated and the reisdue purified by chromatography (Varian Mega Bond Elut®, Si, 5g). Elution with cyclohexane / dichloromethane (1:2) gave the title compound (138mg).

LC/MS ESI R_T 3.70mins MH^+219

Intermediate 12

2-(4-propyl-1,3-thiazol-2-yl)aniline

To a solution of 2-aminobenzenecarbothioamide (714mg) in ethanol (50ml) was added 1-bromo-pentan-2-one (CAS-Number 817-71-0; 976mg). The reaction mixture was stirred for 4h at 80°C and then 16h at room temperature. A white suspension had formed. The solvent was evaporated and the residue partitioned between dichloromethane (30ml) and 2N sodium bicarbonate (40ml). The aqueous phase extracted with dichloromethane (40ml x 2). The combined organic extracts were washed with water (30ml) and brine (30ml) and dried (Na_2SO_4). The solvent was evaporated and the residue purified by (Varian Mega Bond Elut®, Si, 10g). Elution with 15% dichloromethane / cyclohexane gave the title compound as a yellow oil (626mg).

LC/MS ESI R_T 3.72mins MH^+219

Tlc SiO_2 (Cyclohexane / Ethyl acetate 2:1) Rf 0.5

Intermediate 13

2-(4-pentyl-1,3-thiazol-2-yl)aniline (A)

and

2-(5-butyl-4-methyl-1,3-thiazol-2-yl) aniline (B)

To a solution of 2-aminobenzenecarbothioamide (1.73g) in absolute ethanol (60ml) was added 1-bromo-heptan-2-one (CAS No. 16339-93-8;1.9g; This was contaminated with 40% of 3-bromo-heptan-2-one;CAS No. 51134-59-9)

The reaction mixture was stirred for 3.5h at 80°C and then 16h at room temperature. The solvent was evaporated and the residue partitioned between dichloromethane (40ml) and 2N sodium bicarbonate (40ml). The combined organic extracts were washed with water (60ml) and brine (60ml) and dried (Na_2SO_4). The solvent was evaporated to give a mixture of the title compounds (A) and (B) as a yellow oil (1.4g)

NMR ($CDCl_3$ 400MHz; δ) 7.61 (1H, dd, CH), 7.15 (1H, ddd, CH), 6.78- 6.68 (3H, m, 3 x CH), 6.10 (2H, br s, NH_2), 2.78 (2H, t, CH_2), 1.8- 1.2 (6H, m, 3 x CH_2), 0.94 (3H, t, CH_3)

(B) 2.35 (3H, thiazole CH_3)

Intermediate 14

2-(4-butyl-1,3-thiazol-2-yl)aniline

To a solution of 2-aminobenzenecarbothioamide (800mg) in absolute ethanol (50ml) was added 1-bromo-hexan-2-one (CAS-Number 26818-07-5; 1.1g). The reaction mixture was stirred for 4h at 80°C and then 5 days at room temperature. The solvent was evaporated and the residue partitioned between dichloromethane (40ml) and 2N sodium bicarbonate (40ml). The combined organic extracts were washed with water (50ml) and brine (50ml) and dried (Na_2SO_4). The solvent was evaporated and the residue purified by (Varian Mega Bond Elut®, Si, 10g). Elution with 0%-15% dichloromethane / cyclohexane gave the title compound as a yellow oil (677mg)

LC/MS ESI R_T 3.58mins MH^+233

Tlc SiO_2 (Dichloromethane) R_f 0.65

Intermediate 15

2-(2-Aminophenyl)-N,4-dimethyl-1,3-thiazole-5-carboxamide

To a solution of 2-aminobenzenecarbothioamide (411mg) in absolute ethanol (20ml) was added 2-chloro-N-methylacetoacetamide (CAS-number 4116-10-3; 550mg). The resultant yellow solution was stirred at 80°C for 4h and then at room temperature for 18h. A white suspension had formed which was filtered off under vacuum. The filtrate

was concentrated *in vacuo*. The resultant orange oil was partitioned between dichloromethane (40ml) and 2N sodium bicarbonate (40ml). The aqueous phase was extracted with dichloromethane (40ml x 2). The combined organics were washed with water (80ml) and brine (80ml), dried (Na_2SO_4) and concentrated to leave a yellow oil. This was purified by Biotage Flash 40i™, silica. Elution with 1:1, cyclohexane / ethyl acetate afforded the title compound as a yellow oil (45mg)

LC/MS ESI R_T 2.89mins MH^+ 248

Tlc SiO_2 (ethyl acetate / cyclohexane, 1:1) R_f 0.5

Intermediate 16

2-{4-[2-(Benzyloxy)ethyl]-1,3-thiazol-2-yl}aniline

A solution of 4-benzyloxy-1-bromo-2-butanone (7.1g) and 2-aminobenzenecarbothioamide (4g) in DMF (50ml) was heated at 80°C for 3 hours. After cooling to room temperature, the reaction mixture was partitioned between diethyl ether (500ml) and water (100ml). The aqueous layer was separated and extracted with diethyl ether (2X150ml). The organic extracts were combined, dried ($MgSO_4$) and evaporated to give an oily residue which was purified by flash chromatography on silica. Elution with hexane/ethyl acetate 4:1 gave the title compound as a colourless oil (2.0g).

LC/MS ESI R_T 3.88mins MH^+ 311

Intermediate 17

Ethyl [2-(2-aminophenyl)-1,3-thiazol-4-yl]acetate

A mixture of ethyl 4-bromoacetoacetate (2.7g) and 2-aminobenzenecarbothioamide (2g) in DMF (25ml) was heated at 80°C for 2 hours then cooled to room temperature. The reaction mixture was then partitioned between diethyl ether (150ml) and water (200ml). The aqueous layer was separated, extracted with diethyl ether (150ml) then basified to pH 8 with 0.5N aqueous sodium hydroxide then further extracted with diethyl ether (150ml). The organic extracts were combined, dried ($MgSO_4$) and evaporated to give an oily residue which was purified by flash chromatography on silica. Elution with hexane/ethyl acetate 4:1 gave the title compound as a colourless oil (1.46g).

LC/MS ESI R_T 3.39mins MH^+263.1

Intermediate 18

2-Nitrobenzenecarbothioamide

A mixture of *o*-nitrobenzamide (10g) and 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide (15.6g) in toluene (150ml) was heated at reflux for 2 hours then allowed to cool to room temperature. Silica gel (Merck 9385) was then added to the reaction mixture and the solvent was evaporated. The resulting residue, pre-absorbed on silica, was purified by flash chromatography. Elution with cyclohexane/ethyl acetate 3:1 afforded the title compound as a yellow solid (7.9g). NMR ($CDCl_3$ 400MHz; δ) 8.15 (1H,dd,aromatic CH) 7.78 (1H,br s, NH_2) 7.65 (1H,dt,aromatic CH) 7.57-7.51 (2H,m,aromatic CH) 7.09.

Intermediate 19

Ethyl [2-(2-nitrophenyl)-1,3-thiazol-4-yl]acetate

A solution of 2-nitrobenzenecarbothioamide (1g) and ethyl bromoacetoacetate (1.15g) in DMF (10ml) was heated at 80°C for 2 hours then cooled to room temperature. The mixture was then partitioned between water (100ml) and diethyl ether (200ml). The aqueous phase was separated and extracted with diethyl ether (100ml). The combined organic layers were dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography. Elution with cyclohexane-ethyl acetate 3/1 gave the title compound (1.15g).

LC/MS ESI R_T 3.21mins MH^+293

Intermediate 20

[2-(2-Nitrophenyl)-1,3-thiazol-4-yl]acetaldehyde

To a solution of ethyl [2-(2-nitrophenyl)-1,3-thiazol-4-yl]acetate (150mg) in dichloromethane (3ml) at –78°C was added a 1M solution of diisobutylaluminum hydride in toluene (0.77ml) over 10 mins. The reaction mixture was stirred at -78°C for 2 hours then treated with methanol (1ml) and allowed to warm-up to room temperature. A saturated aqueous solution of potassium sodium tartrate (3ml) was added and the resulting mixture was stirred at room temperature for 2 hours. The reaction mixture was

then partitioned between diethyl ether (200ml) and water (150ml). The aqueous layer was separated and extracted with diethyl ether (50ml). The combined organic layers were dried ($MgSO_4$) and evaporated to afford the title compound (130mg).
LC/MS ESI R_T 2.49mins MH^+249.3

Intermediate 21

(*R*)-4-(1-Hydroxylethyl)-2-(2-nitrophenyl)-1,3-thiazole

A 1.6M solution of n-butyl lithium in hexanes (93.6ml) was added to diisopropylamine (20.5ml) in THF (30ml) at -70°C. The resulting cloudy solution was stirred at that temperature for 20 mins. A solution of chloroacetic acid (7.0g) in THF (70ml) was then slowly added over 70 mins, the temperature being kept between -60 °C and -70 °C throughout the addition. After stirring for a further hour at -70 °C, the anionic solution was carefully transferred *via* cannula to a solution of methyl (*R*)-lactate in THF (50ml) at 0 °C. The temperature inside the reaction vessel dropped to -10 °C after completion of the addition. The reaction mixture was then cooled to -70 °C and stirred at that temperature for 30mins before being carefully quenched with acetic acid (15ml). After slowly warming up to room temperature over 16 hours, the white slurry was partitioned between ethyl acetate (300ml) and water (200ml). The aqueous layer was separated and extracted with ethyl acetate (200ml). The combined organic extracts were washed with saturated aqueous sodium bicarbonate (2X100ml), dried ($MgSO_4$) and evaporated to give an oily residue (1.4g).

The acid chloride thus obtained was added to a solution of 2-nitrobenzamidecarbothioamide (1g) in DMF (30ml) and the resulting solution was stirred at 80°C for 2 hours before being cooled to room temperature. The reaction mixture was diluted with ether (300ml) and washed with water (100ml). The aqueous was re-extracted with ether (2X150ml). The combined organic extracts were evaporated to give a crude oil that was then purified by two successive flash column chromatographies. Elution with ethyl acetate/cyclohexane 1:3 and increasing the polarity to neat ethyl acetate, afforded the title compound (583mg) as a yellow oil.
LCMS R_T 2.82mins (not ionised well)

NMR (d^6DMSO 400MHz; δ) 7.96 (1H,d,aromatic CH) 7.88 (1H,d,aromatic CH) 7.79 (1H,t,aromatic CH) 7.72 (1H,t,aromatic CH) 7.59 (1H,s,thiazole CH) 5.42 (1H,d,OH) 4.80 (1H,p,CHOH) 1.36 (3H,d,CH_3)

Intermediate 22

4-(2,2-Difluoroethyl)-2-(2-nitrophenyl)-1,3-thiazole

A solution of [2-(2-nitrophenyl)-1,3-thiazol-4-yl]acetaldehyde (130mg) and (diethylamino)sulfur trifluoride (0.131ml) in dichloromethane (1ml) was stirred at room temperature for 2 hours 20 mins. More (diethylamino)sulfur trifluoride (0.05ml) was then added and the solution was stirred at room temperature for a further 2 hours. The reaction mixture was then diluted with dichloromethane (100ml) and washed with saturated aqueous sodium bicarbonate (50ml). The aqueous phase was separated, extracted with dichloromethane (50ml). The combined organic extracts were dried ($MgSO_4$) and evaporated. The resulting crude material was purified by flash chromatography. Elution with ethyl acetate/hexane 1:3 gave the title compound as a colourless oil (72mg).

LC/MS ESI R_T 3.24mins MH^+271

Intermediate 23

2-[4-(2,2-Difluoroethyl)-1,3-thiazol-2-yl]aniline

A mixture of 4-(2,2-difluoroethyl)-2-(2-nitrophenyl)-1,3-thiazole (68.5mg) and 10% palladium hydroxide on carbon (130mg) in ethanol (3ml) was treated with hydrogen over 3 hours. The catalyst was filtered off over the filter agent Celite® and the filtrate was evaporated to give the title compound as a yellow oil (46.5mg).

LC/MS ESI R_T 3.40mins MH^+241.3

Intermediate 24

Ethyl 2-(2-aminophenyl)-1,3-thiazole-4-carboxylate

To a solution of 2-aminobenzenecarbothioamide (1.01g) in anhydrous DMF (12.5ml) was added dropwise ethylbromopyruvate (1.10g). The solution was stirred at 80°C for 1.5 hours. The resultant mixture was cooled and partitioned between ethyl acetate (3x50ml) and water (50ml). The combined organics were evaporated and the residue purified by flash chromatography.Elution with hexane : ethyl acetate (9:1) gave the title compound (657mg)

NMR (DMSO, 400MHz; δ) 8.47 (1H,s,aromatic CH) 7.58 (1H,d,aromatic CH) 7.18 (1H,dd,aromatic CH) 7.10 (2H,br s,NH_2) 6.82 (1H,d,aromatic CH) 6.62 (1H,dd,aromatic CH) 4.34 (2H,q,CH_2) 1.33 (3H,t,CH_3)

Intermediate 25

2-(2-Aminophenyl)-1,3-thiazole-4-carboxylic acid

Ethyl 2-(2-aminophenyl)-1,3-thiazole-4-carboxylate (198mg) was dissolved in ethanol (15ml) by heating to 50°C. Water (1ml) and potassium hydroxide (225mg) were added and the suspension was stirred at 54°C for 3 hours. The mixture was evaporated and partitioned between water (25ml) and ethyl acetate (25ml). The aqueous layer was acidified to pH 1 using hydrochloric acid (2N, aqueous). Further ethyl acetate (25ml) was added to dissolve the precipitate. The layers were separated and the aqueous layer further extracted with ethyl acetate (2x25ml). The combined organics were washed with brine (25ml), and then evaporated to dryness. The solid was triturated with ethyl acetate to yield the title compound (245mg, contaminated with sodium chloride).

NMR (DMSO, 400MHz, δ) 8.39 (1H,s,aromatic CH) 7.59 (1H,br d,aromatic CH) 7.17 (1H,br t,aromatic CH) 7.12 (2H,br s,NH_2) 6.84 (1H,d,aromatic CH) 6.62 (1H,aromatic CH)

Intermediate 26

2-(2-Aminophenyl)-N-methyl-1,3-thiazole-4-carboxamide

A suspension of 2-(2-aminophenyl)-1,3-thiazole-4-carboxylic acid (140mg), WSCDI (112µl), hydroxybenzotriazole (90.2mg) in tetrahydrofuran (2ml) was stirred at 20°C under nitrogen for 45 minutes before adding methylamine (2M in tetrahydrofuran,

335µl). The mixture was stirred for 2 hours at 20°C then diluted with dichloromethane (20ml). This mixture was washed with hydrochloric acid (2M, 20ml), sodium bicarbonate (1M, 20ml) and the organic layer evaporated to yield the title compound (11mg). The aqueous hydrochloric acid layer was basified to pH 8 using sodium bicarbonate (70ml) and extracted using dichloromethane (3 x 20ml). The combined organics were dried ($MgSO_4$) and evaporated to yield the title compound (60.3mg). LC/MS ESI R_T 2.89mins MH^+234

Intermediate 27

2-(4-Cyclobutyl-1,3-thiazol-2-yl)aniline

A solution of 2-bromo-1-cyclobutylethanone (CAS number 128312-69-6, 354mg) in absolute alcohol (5ml) was added dropwise to a solution of 2-aminobenzenecarbothioamide (152mg) in absolute alcohol (5ml) and the resulting mixture was heated at 80°C under nitrogen for 3h. A few drops of concentrated hydrochloric acid were added and the mixture was heated for a further 2h. The solvent was removed and the residue was partitioned between sodium bicarbonate (8%) and ethyl acetate. The combined organic extracts were washed with brine and dried (Na_2SO_4) and the solvent was evaporated. The residue was purified (Varian Mega Bond Elut®) using cyclohexane (x3) and dichloromethane (x3) as eluant. The appropriate fractions were concentrated *in vacuo* to give the title compound (198mg). LC/MS ESI R_T 4.0mins MH^+ 231

Intermediate 28

2-(4-Cyclohexyl-1,3-thiazol-2-yl)aniline

A solution of 2-bromo-1-cyclohexylethanone (CAS number 56077-28-2, 354mg) in absolute alcohol (5ml) was added dropwise to a solution of 2-aminobenzenecarbothioamide (152mg) in absolute alcohol (5ml) and the resulting mixture was heated at 80°C under nitrogen for 6h. The solvent was removed and the residue was partitioned between sodium bicarbonate (8%) and ethyl acetate. The combined organic extracts were washed with brine and dried (Na_2SO_4) and the solvent was evaporated. The residue was purified (Varian Mega Bond Elut®, Si) using

cyclohexane (x3) and dichloromethane (x3) as eluant. This gave the title compound (167mg).

LC/MS ESI R_T 4.21mins MH^+ 259

Intermediate 29

2-(4-Cyclopentyl-1,3-thiazol-2-yl)aniline

A solution of 2-bromo-1-cyclopentylethanone (CAS number 52423-62-8, 191mg) in absolute alcohol (5ml) was added to a solution of 2-aminobenzenecarbothioamide (152mg) in absolute alcohol (5ml) and the resulting mixture was heated at 80°C under nitrogen for 6h. The solvent was removed and the residue was partitioned between sodium bicarbonate (8%) and ethyl acetate. The combined organic extracts were washed with brine and dried (Na_2SO_4) and the solvent was evaporated. The residue was purified (Varian Mega Bond Elut®, Si) using cyclohexane (x3) and dichloromethane (x3) as eluant. This gave the title compound (60mg).

LC/MS ESI R_T 4.05mins MH^+ 245

Intermediate 30

1-Bromo-3-cyclopropylacetone

Bromine (0.58ml) was added in a slow and steady stream to a solution of 1-cyclopropylacetone [may be prepared by literature methods, such as described in Yoshio Ueno *et al*, Tetrahedron Lett. (1982), 23(25), 2577-80] (1.1052g) in dry methanol (9ml) at –10°C. The solution was warmed to 7°C and stirred for 40mins, then hydrogen chloride (1M in diethyl ether; 0.25ml) was added and the mixture stirred for 3.5h at 5-10°C. To the reaction was added aqueous sodium thiosulphate solution (1M; 6ml) dropwise until decolourisation occurred followed by water (2ml). The reaction was extracted into diethyl ether (x2) and the combined organics were washed with saturated aqueous sodium bicarbonate solution and brine, dried over anhydrous magnesium sulphate, filtered and evaporated in vacuo to give the title compound as a light yellow oil (1.1g)

NMR ($CDCl_3$ 400MHz; δ) 3.96 (2H,s,CH_2) 2.56 (2H,d,CH_2) 1.03 (1H,m,CH) 0.61 (2H,m,CH_2) 0.18 (2H,m,CH_2)

Intermediate 31

2-[4-(Cyclopropylmethyl)-1,3-thiazol-2-yl]aniline

1-Bromo-3-cyclopropylacetone (500mg) in absolute ethanol (14ml) was added to a solution of 2-aminobenzenecarbothioamide (430mg) in absolute ethanol (14ml). The mixture was stirred for 6.5h at 80°C under nitrogen, cooled to room temperature and evaporated in vacuo. The residue was partitioned between ethyl acetate (x2) and saturated aqueous sodium bicarbonate solution. Combined organics were washed with brine, dried over anhydrous magnesium sulphate, filtered and concentrated in vacuo. The oil was purified by Varian Mega Bond Elut® (Si, 10g); elution with 0-6% dichloromethane in cyclohexane gave the title compound as a yellow oil (248mg).

LC/MS ESI R_T 3.88mins MH^+ 231

Intermediate 32

1-Bromo-4-methylpentan-2-one

Bromine (0.77ml) was added in a slow and steady stream to a solution of 4-methyl-2-pentanone (1.5g) in dry methanol (12ml) at –10°C. The solution was warmed to 7°C and stirred for 1h. To the reaction was added aqueous sodium thiosulphate solution dropwise until decolourisation occurred followed by saturated aqueous sodium bicarbonate solution until neutral. The reaction was extracted into diethyl ether (x2) and the combined organics were washed with brine, dried over anhydrous magnesium sulphate, filtered and evaporated in vacuo to give the title compound as a colourless oil (2.1g)

NMR ($CDCl_3$ 400MHz; δ) 3.88 (2H,s,CH_2Br) 2.54 (2H,d,CH_2) 2.18 (1H,m,CH) 0.93 (6H,d,2xCH_3)

Intermediate 33

2-(4-Isobutyl-1,3-thiazol-2-yl)aniline

1-bromo-4-methylpentan-2-one (500mg) in absolute ethanol (14ml) was added to a solution of 2-aminobenzenecarbothioamide (426mg) in absolute ethanol (14ml). The mixture was stirred for 5h at 80°C under nitrogen, cooled to room temperature and evaporated in vacuo. The residue was partitioned between ethyl acetate (x2) and saturated aqueous sodium bicarbonate solution. Combined organics were washed with brine, dried over anhydrous magnesium sulphate, filtered and evaporated in vacuo. The oil was purified by Varian Mega Bond Elut® (Si, 10g); elution with cyclohexane followed by 0-3% dichloromethane in cyclohexane gave the title compound as a yellow oil (560mg).

LC/MS ESI R_T 4.02mins MH^+ 233

Intermediate 34

(*R*)-2-[4-(1-Hydroxyethyl)-1,3-thiazole-2-yl]aniline

A mixture of (*R*)-4-(1-hydroxylethyl)-2-(2-nitrophenyl)-1,3-thiazole (100mg) and 10% palladium hydroxide on carbon (80mg) in ethanol (4ml) was treated with hydrogen over 3 hours. The catalyst was filtered off over the filter agent Celite® and the filtrate was evaporated to give the title compound as a pale brown oil (83.3mg).

LC/MS R_T 2.93mins (not ionised well)

NMR (d^6DMSO 400MHz; δ) 7.60 (1H,d,aromatic CH) 7.14 (1H,t,aromatic CH) 7.03 (1H,s,thiazole CH) 6.76-6.67 (2H,m,aromatic 2XCH) 6.04 (2H,br. s,NH_2) 5.01 (1H,q,CHOH) 2.53 (1H,br.s,OH) 1.60 (3H,d,CH_3)

Intermediate 35

4-Fluoro-2-nitrobenzenecarbothioamide

A mixture of 4-fluoro-2-nitrobenzamide (1.42g), 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane 2,4-disulfide (2.11g), and toluene (30ml) was heated at reflux under nitrogen for 3h. The cooled mixture was concentrated and the residue adsorbed from ethyl acetate (35ml) onto silica gel (Merck 7734, 24ml). The resultant silica was purified by applied as a solid plug to a Biotage Flash™, silica column (90g), and this

eluted with ethyl acetate-cyclohexane (gradient 1:19 to 3:7) to give the title compound as orange crystals (869mg).

LC/MS ESI R_T 2.45mins, MH^+199.

Intermediate 36

5-Fluoro-2-nitrobenzenecarboamide

A solution of 5-fluoro-2-nitrobenzoic acid (10g) and 1,1 carbonyldiimidazole (9.5g) in THF (90ml) was stirred for 1.5 hours at room temperature. 2M methanolic ammonia (40ml) was added and the resulting solution was stirred for another 18 hours. The solvents were evaporated, then ethyl acetate (150ml) and water (150ml) were added. The aqueous layer was separated and extracted with ethyl acetate (150ml). The organic fractions were combined, dried over $MgSO_4$ and evaporated to leave a yellow oil which was purified by flash column chromatography with a 2:1 hexane/ethyl acetate eluent. The title compound was obtained as a yellow solid (2.49g).

LCMS R_T 1.02mins (not ionised well)

Tlc SiO_2 (1:1 ethyl acetate/hexane) R_f 0.24

Intermediate 37

5-Fluoro-2-nitrobenzenecarbothioamide

To a solution of 2,4-bis(4-methoxyphenyl)1,3-dithia-2,4-diphosphetane-2,4-disulfide (2.1g) in toluene (30ml), 5-fluoro-2-nitrobenzenecarboamide in toluene (20ml) was added. The reaction mixture was heated at reflux for 2 hours, then cooled to room temperature. DCM (100ml) was added and the crude residue was evaporated onto silica gel. The residue was purified by flash column chromatography (solid loading). Elution with hexane/ethyl acetate 4:1 and increasing the polarity to neat ethyl acetate. After evaporation the title compound was obtained as a yellow solid (2.17g)

LC R_T 2.42mins (not ionised well)

Tlc SiO_2 (1:1 ethyl acetate/hexane) R_f 0.42

Intermediate 38

2-(4-Fluoro-2-nitrophenyl)-4-methyl-1,3-thiazole

1-Chloro-2-propanone (420µl) was added dropwise under nitrogen to a stirred solution of 4-fluoro-2-nitrobenzenecarbothioamide (869mg) in ethanol (16ml) and the solution heated at reflux for 6h. The solution was evaporated, treated with aqueous 1M sodium carbonate (25ml), and extracted with ethyl acetate (2x25ml). The combined, dried (Na_2SO_4) organic extracts were evaporated, and the residue absorbed from ethyl acetate (20ml) onto silica gel (Merck 7734, 6g). The resultant silica gel was applied to a Biotage Flash™, silica column (40g), and this eluted with ethyl acetate-cyclohexane (1:9) to give the title compound as cream crystals (781mg).

LC/MS ESI R_T 3.21mins MH^+ 239.

Intermediate 39

4-Ethyl-2-(5-fluoro-2-nitrophenyl)-1,3-thiazole

To a solution of 5-fluoro-2-nitrobenzenecarbothioamide (1.17g) in DMF (20ml), 1-bromo-2-butanone was added and the reaction was heated at reflux for 1.5 hours. The reaction mixture was cooled and partitioned between diethyl ether (100ml) and water (100ml). The aqueous layer was extracted with a further portion of diethyl ether (100ml), then basified to pH 8 with NaOH and extracted with diethyl ether (100ml) The organics were combined, dried over $MgSO_4$ and evaporated to leave the a crude yellow oil. The oil was purified by flash column chromatography using 4:1 hexane/ethyl acetate eluent. The title compound was obtained as a yellow oil (1.48g).

LC/MS ESI R_T 3.23mins MH^+ 253

Intermediate 40

4-Ethyl-2-(5-hydroxy-2-nitrophenyl)-1,3-thiazole

To a solution of 4-ethyl-2-(5-fluoro-2-nitrophenyl)-1,3-thiazole (0.9g) in DMSO (5ml) a solution of NaOH (1.3g) in aqueous DMSO (275ml;10%(v/v) H_2O) was added. The reaction mixture was heated at reflux for 1.5 hours then cooled to room temperature. The reaction mixture was evaporated to leave a crude white solid which was purified by flash column chromatography using a 3:1 hexane/ethyl acetate eluent. The title compound was obtained as a white solid (0.8g).

LC/MS ESI R_T 3.19mins MH^+ 251

Intermediate 41

5-Fluoro-2-(4-methyl-1,3-thiazol-2-yl)aniline

A solution of 2-(4-fluoro-2-nitrophenyl)-4-methyl-1,3-thiazole (781mg) in ethanol (20ml) was added to a suspension of pre-hydrogenated 10% palladium-on-carbon (50% paste with water) (300mg) in ethanol (35ml) and hydrogenated at 23° and atmospheric pressure until hydrogen uptake ceased (after 230ml). The catalyst was filtered off (hyflo) and the filtrate evaporated to give the title compound as cream crystals (600mg).

LC/MS ESI R_T 3.62mins, MH^+ 209.

Intermediate 42

2-(4-Ethyl-1,3-thiazol-2-yl)-4-fluoroaniline

A solution of 4-ethyl-2-(5-fluoro-2-nitrophenyl)-1,3-thiazole (0.2g) in ethanol (2.5ml) was added to wet $Pd(OH)_2$ on charcoal under vacuum. The reaction mixture was placed under hydrogen and stirred for 1 hour at room temperature. The crude material obtained was filtered through Celite® and evaporated to leave the title compound as a yellow oil (168mg).

LC/MS ESI R_T 3.70mins MH^+ 223

Intermediate 43

2-(4-Ethyl-1,3-thiazol-2-yl)-4-hydroxyaniline GW697266X

A solution of 4-ethyl-2-(5-hydroxy-2-nitrophenyl)-1,3-thiazole (0.2g) in ethanol (2.5ml) was added to wet $Pd(OH)_2$ on charcoal under vacuum. The reaction mixture was placed under hydrogen and stirred for 1 hour at room temperature. The crude material obtained was filtered through Celite® and evaporated to leave the title compound as a white solid (0.17g).

LCMS ESI R_T 2.94mins MH^+ 221

Intermediate 44

tert-Butyl 3-bromo-4-oxopiperidine-1-carboxylate

To a solution of tert-butyl 4-oxopiperidine -1-carboxylate (7.11g) in diethyl ether (140ml) was added 5,5-dibromobarbituric acid (5g). The mixture was stirred for 3 days at room temperature under nitrogen. The reaction was filtered, the filtrate evaporated and the solid purified by flash column chromatography on 230-400 mesh silica. Elution with cyclohexane / ethyl acetate 5:1 gave the title compound as a white solid (6.98g). Anal. Calcd for $C_{10}H_{16}BrNO_3$ 0.25 H_2O: C, 42.49; H, 5.88; N, 4.96. Found: C, 42.52; H, 5.61; N, 5.02.

Intermediate 45

tert-Butyl 2-(2-aminophenyl)-6,7-dihydro[1,3]thiazolo[5,4-c]pyridine-5(4H)-carboxylate

Tert-butyl 3-bromo-4-oxopiperidine-1-carboxylate (177mg) in absolute ethanol (5ml) was added to a solution of 2-aminobenzenecarbothioamide (97mg) in absolute ethanol (5ml). The mixture was stirred for 2.25h at 80°C under nitrogen and then cooled to room temperature. Triethylamine (0.355ml) was added, the reaction evaporated in vacuo and the residue partitioned between ethyl acetate (x2) and water. Combined organics were washed with brine, dried over anhydrous magnesium sulphate, filtered and evaporated in vacuo. The residue was purified by Varian Mega Bond Elut® (Si, 5g); elution with 0-90% dichloromethane in cyclohexane gave the title compound as a yellow residue (41mg).

LC/MS ESI R_T 3.92mins MH^+ 332

Intermediate 46

2-(5,6-Dihydro-4H-cyclopenta[d][1,3]thiazol-2-yl)aniline

2-Chlorocyclopentanone (779mg) in absolute ethanol (32ml) was added to a solution of 2-aminobenzenecarbothioamide (1g) in absolute ethanol (32ml). The mixture was stirred for 2h at 80°C under nitrogen, cooled to room temperature and stirred for a further 18h. Reaction evaporated in vacuo and the residue partitioned between ethyl acetate (x2) and saturated aqueous sodium bicarbonate solution. Combined organics were washed with brine, dried over anhydrous magnesium sulphate, filtered and concentrated in vacuo. The residue was purified by Varian Mega Bond Elut® (Si,

10g); elution with 0-60% dichloromethane in cyclohexane gave the title compound as a dark yellow solid (104mg).

LC/MS ESI R_T 3.72mins MH^+ 217

Intermediate 66

tert-Butyl 4-(hydroxymethyl)piperidine-1-carboxylate

Triethylamine (48ml) was added to a solution of 4-(hydroxymethyl)piperidine (20g) in dry dichloromethane (100ml) under nitrogen. Di-tert-butyl dicarbonate (42.4g) in dry dichloromethane (50ml) was added dropwise and the mixture was stirred at room temperature for 18h. The solvent was removed and the residue was partitioned between water (100ml) and ethyl acetate (100ml). The organic extracts were washed with water, hydrochloric acid (2M) and brine and were dried ($MgSO_4$). The solvent was evaporated and the residue was dried under vacuum to give the title compound as a white solid (31.4g).

MS MH^+ 216, (Thermospray).

Intermediate 67

tert-Butyl (2R,6R)-2,6-dimethyl-4-methylenepiperidine-1-carboxylate

Potassuim tert-butoxide (0.83g) was added in one portion to a suspension of methyl triphenylphosphonium bromide 93.1g) in dry THF (20ml) at 0°C under nitrogen. The mixture was stirred for 20mins then a solution of tert-butyl (2R,6R)-2,6-dimethyl-4-piperidone-1-carboxylate (CAS 146337-38-4) (1.33g) in dry THF (5ml) was added dropwise over 3 mins at 0°C. The mixture was stirred at 0°C for 0.5h, then allowed to warm to room temperature and stirred for 16h. The mixture was partitioned between water (50ml) and ethyl acetate (3x50ml). The combined organic extracts were dried ($MgSO_4$). The solvent was evaporated and the residue purified by Biotage Flash™, silica. Elution with cyclohexane / ethyl acetate 20:1 gave the title compound as a colourless oil (0.7g)

Tlc (Cyclohexane / ethyl acetate 20:1) R_f 0.20;

Intermediate 68

tert-Butyl (2R,6R)-4-(hydroxymethyl)-2,6-dimethylpiperidine-1-carboxylate

Borane (1M in THF;12ml) was added dropwise to a solution of 2-methyl-2-butene 92.6ml) at 0oC under nitrogen. The solution was stirred for 1h at 0°C, then a solution of tert-Butyl (2R,6R)-2,6-dimethyl-4-methylenepiperidine-1-carboxylate (684mg) in dry THF (5ml) was added dropwise at 0°C. The mixture was stirred at 0°C for 0.5h, then at room temperature for 3h. Water (0.5ml), methanol (6ml) and sodium hydroxide solution (2M; 6ml) were then sequentially added. The mixture was re-cooled to 0°C, then hydrogen peroxide (27%;2.6ml) was added dropwise over 2mins and the mixture stirred at room temperature for 16h. The mixture was acidified to pH 4 with HCl (2M; ca 6ml) then basified to pH 12 with sodium carbonate (2M; ca 10ml). The mixture was extracted with ethyl acetate (3x20ml) and the combined extracts dried ($MgSO_4$). The solvent was evaporated to give the title compound as a colourless oil (0.7g)
NMR ($CDCl_3$ 400MHz; δ) 4.20 (1H, m,CH) 3.84 (1H, m, CH) 3.52 (2H, m, CH2) 2.02 (1H, m, CH) 1.75-1.54 (2H, m, CH_2 EQ+AX) 1.48 (9H, s, 3xCH3) 1.28 (3H, d, CH3) 1.20 (4H,d+br d,CH_3+CH EQ) 0.91 (1H,dd, CH AX)

Intermediate 69

trans-1-Benzyl-2,6-dimethyl-4-methylenepiperidine

Potassium tert-butoxide (0.27g) was added in one portion to a suspension of methyl triphenylphosphonium bromide (1.01g) in dry THF (10ml) at 0°C under nitrogen. The mixture was stirred for 20mins then a solution of trans-2,6-dimethyl-1-(phenylmethyl)-4-Piperidinone (CAS 198211-14-2) (0.41g) in dry THF (5ml) was added dropwise over 3 mins at 0oC. The mixture was stirred at 0°C for 0.5h, then allowed to warm to room temperature and stirred for 16h. The mixture was partitioned between water (50ml) and ethyl acetate (3x50ml). The combined organic extracts were dried ($MgSO_4$). The solvent was evaporated and the residue purified by chromatography on silica. Elution with cyclohexane / ethyl acetate 9:1 gave the title compound as a colourless oil (0.4g)
NMR ($CDCl_3$ 400MHz; δ) 7.39 (2H, br d,aromatic 2xCH) 7.29 (2H, br t, aromatic 2xCH) 7.19 (1H, br t, aromatic CH) 4.68 (2H, s, 2xCH) 3.92,3.45 (2H, 2xd, CH_2) 2.92 (2H, m, 2xCH) 2.30 (2H, dd, CH_2) 1.96 (2H, dd,CH_2) 0.99 (6H, d, 2xCH_3)

Intermediate 70

[(2alpha,6beta)-1-benzyl-2,6-dimethylpiperidin-4-yl]methanol

Borane (1M in THF;3.72ml) was added dropwise to a solution of 2-methyl-2-butene (0.8ml) at 0°C under nitrogen. The solution was stirred for 1h at 0°C, then a solution of trans-1-benzyl-2,6-dimethyl-4-methylenepiperidine (200mg) in dry THF (2ml) was added dropwise at 0°C. The mixture was stirred at 0°C for 0.5h, then at room temperature for 3h. Water (0.1ml), methanol (2ml) and sodium hydroxide solution (2M; 1.9ml) were then sequentially added. The mixture was re-cooled to 0°C, then hydrogen peroxide (27%;0.8ml) was added dropwise over 2mins and the mixture stirred at room temperature for 16h. The mixture was acidified to pH 4 with HCl (2M; ca 2ml) then basified to pH 12 with sodium carbonate (2M; ca 3ml). The mixture was extracted with ethyl acetate (3x15ml) and the combined extracts dried ($MgSO_4$). The solvent was evaporated to give the title compound as a colourless oil (0.272g)

MS Found MH^+ 234 (thermospray)

NMR ($CDCl_3$ 400MHz; δ) 7.38 (2H, br d, aromatic 2xCH), 7.29 (2H, br t, aromatic 2xCH) 7.21 (1H, br t, aromatic CH) 3.94 (1H, br d, 0.5xCH2) 3.48-3.38 (3H, 2xd, 0.5CH+CH2) 3.02 (1H,m,CH) 2.87 (1H, m, CH) 1.90 (1H, m, CH) 1.64 (1H, br d, CH EQ) 1.42 (1H, br m, CH AX) 1.10-1.05 (2H, m, CH_2) 0.95,0.90 (6H, 2xd, $2xCH_3$)

Intermediate 71

cis-1-Benzyl-2,6-dimethyl-4-methylenepiperidine

Potassuim tert-butoxide (1.91g) was added in one portion to a suspension of methyl triphenylphosphonium iodide (7.14g) in dry THF (50ml) at 0°C under nitrogen. The mixture was stirred for 20mins then a solution of cis-2,6-dimethyl-1-(phenylmethyl)-4-piperidinone (CAS 198211-15-3) (2.93g) in dry THF (10ml) was added dropwise over 2 mins at 0°C. The mixture was stirred at 0°C for 0.5h, then allowed to warm to room temperature and stirred for 16h. The mixture was partitioned between ammonium chloride solution (50ml) and ethyl acetate (3x50ml). The combined organic extracts were dried ($MgSO_4$). The solvent was evaporated and the residue purified by chromatography on silica. Elution with ether gave the title compound as a colourless oil (2.6g)

NMR ($CDCl_3$ 400MHz; δ) 7.39 (2H, br d,aromatic 2xCH) 7.29 (2H, br t, aromatic 2xCH) 7.19 (1H, br t, aromatic CH) 4.62 (2H, s, 2xCH) 3.80 (2H, s, CH_2) 2.65 (2H, m, 2xCH) 2.17 (2H, dd, CH_2) 2.05 (2H, br t,CH_2) 1.10 (6H, d, $2xCH_3$)

Intermediate 72

[(2alpha,4beta,6alpha)-1-benzyl-2,6-dimethylpiperidin-4-yl]methanol isomer 2 (A) and [(2alpha,4alpha,6alpha)-1-benzyl-2,6-dimethylpiperidin-4-yl]methanol isomer 2 (B)

Borane (1M in THF;25.6ml) was added dropwise to a solution of 2-methyl-2-butene (5.4ml) at 0°C under nitrogen. The solution was stirred for 1h at 0°C, then a solution of cis-1-benzyl-2,6-dimethyl-4-methylenepiperidine (1.3g) in dry THF (10ml) was added dropwise at 0°C. The mixture was stirred at 0°C for 0.5h, then at room temperature for 3h. Water (0.7ml), methanol (13ml) and sodium hydroxide solution (2M; 0.5ml) were then sequentially added. The mixture was re-cooled to 0°C, then hydrogen peroxide (27%;5.5ml) was added dropwise over 10mins and the mixture stirred at room temperature for 16h. The mixture was acidified to pH 4 with HCl (2M; ca 10ml) then basified to pH 12 with sodium carbonate (2M; ca 20ml). The mixture was extracted with ethyl acetate (3x50ml) and the combined extracts dried ($MgSO_4$). The solvent was evaporated and the residue purified by chromatography on silica. Elution with dichloromethane / ethanol / ammonia 300:8:1 gave the title compound (A) as a colourless oil (0.461mg)

NMR ($CDCl_3$ 400MHz) 7.38δ (2H, br d, CH_s), 7.30δ (2H, br t, CH_s) 7.20δ (1H, br t, aromatic CH) 3.80δ (2H, s, CH_2) 3.60δ (2H, d, CH_2) 2.82δ (2H,m,2xCH) 1.98δ (1H, m, CH) 1.62-1.50δ (4H, m, $2xCH_2$) 1.02δ (6H, d, $2xCH_3$)

And the title compound (B) as a colourless oil (134mg)

NMR ($CDCl_3$ 400MHz) 7.38δ (2H, br d, CH_s), 7.34δ (2H, br t, CH_s) 7.18δ (1H, br t, aromatic CH) 3.80δ (2H, s, CH_2) 3.43δ (2H, d, CH_2) 2.55δ (2H,m,2xCH) 1.70δ (2H, br d, CH_2 EQ) 1.14-1.00δ (8H, d+m, $2xCH_3$ + CH_2 AX)

Intermediate 80

tert-Butyl 4-({[({2-[4-methyl-1,3-thiazol-2-yl]phenyl}amino)carbonyl]oxy}methyl)piperidine-1-carboxylate

A mixture of tert-butyl 4-(hydroxymethyl)piperidine-1-carboxylate (CAS No.123855-51-6;186mg) and diisopropylethylamine (0.12ml) in dry THF (1ml) was added dropwise to a solution of triphosgene (128mg) in dry THF (1ml) at 0-5°C under nitrogen. The mixture was stirred for 1 hr, then a solution of 2-(4-methyl-1,3-thiazol-2-

yl)aniline (164mg) in THF (1ml) containing diisopropylethylamine (0.12ml) was added dropwise and the mixture stirred for 16 hr at room temperature. The mixture was treated with 10ml of saturated sodium bicarbonate solution and 10 ml of water, stirred for 0.5h, and then extracted into dichloromethane and dried over $MgSO_4$. The solvent was evaporated and the residue purified by chromatography (Biotage Flash™,). Elution with cyclohexane / ethyl acetate (10:1) gave the title compound as a white solid (205mg.)

LC/MS ESI R_T 4.29mins MH^+ 432

Intermediate 81

tert-Butyl 4-({[({2-[4-trifluoromethyl-1,3-thiazol-2-yl]phenyl}amino)carbonyl]oxy}methyl) piperidine-1-carboxylate

A mixture of tert-butyl 4-(hydroxymethyl)piperidine-1-carboxylate (CAS No.123855-51-6;48mg) and diisopropylethylamine (50ul) in dry THF (1ml) was added dropwise to a solution of triphosgene (33mg) in dry THF (1ml) at 0-5°C under nitrogen. The mixture was stirred for 1 hr, then a solution of 2-(4-trifluoromethyl-1,3-thiazol-2-yl)aniline (55mg) in THF (1ml) containing diisopropylethylamine (50ul) was added dropwise and the mixture stirred for 16 hr at room temperature. The mixture was treated with 5ml of saturated sodium bicarbonate solution and 5 ml of water, stirred for 0.5h, and then extracted into dichloromethane and dried over $MgSO_4$. The solvent was evaporated and the residue purified by chromatography (Biotage Flash™). Elution with cyclohexane / ethyl acetate (4:1) gave the title compound as a yellow solid (63mg.)

LC/MS ESI R_T 4.08mins MH^+ 486

Intermediate 82

tert-Butyl 4-({[({2-[4-cyclopropyl-1,3-thiazol-2-yl]phenyl}amino)carbonyl]oxy}methyl) piperidine-1-

A mixture of tert-butyl 4-(hydroxymethyl)piperidine-1-carboxylate (CAS 123855-51-6;370mg) and diisopropylethylamine (0.24ml) in dry THF (5ml) was added dropwise to a solution of triphosgene (256mg) in dry THF (3ml) at 0-5°C under nitrogen. The mixture was stirred for 1 hr, then a solution of 2-(4-cyclopropyl-1,3-thiazol-2-yl)aniline (371mg) in THF (5ml) containing diisopropylethylamine (0.24ml) was added dropwise

and the mixture stirred for 16 hr at room temperature. The mixture was treated with 10ml of saturated sodium bicarbonate solution and 10ml of water, stirred for 0.5h, and then extracted into dichloromethane and dried over $MgSO_4$. The solvent was evaporated and the residue purified by chromatography (Biotage Flash™, silica, 90g). Elution with cyclohexane / ethyl acetate (6:1) gave the title compound as a white solid (380mg.)

LC/MS ESI R_T 4.37mins MH^+ 458

Intermediate 83

tert-Butyl 4-{[({[2-(4-phenyl-1,3-thiazol-2-yl)phenyl]amino}carbonyl)oxy]methyl}piperidine-1-carboxylate

A mixture of tert-butyl 4-(hydroxymethyl)piperidine-1-carboxylate (CAS 123855-51-6;48mg) and diisopropylethylamine (50ul) in dry THF (1ml) was added dropwise to a solution of triphosgene (33mg) in dry THF (1ml) at 0-5°C under nitrogen. The mixture was stirred for 1 hr, then a solution of 2-(4-phenyl-1,3-thiazol-2-yl)aniline (67mg) in THF (1ml) containing diisopropylethylamine (50uL) was added dropwise and the mixture stirred for 16 hr at room temperature. The mixture was treated with 4ml of saturated sodium bicarbonate solution and 4 ml of water, stirred for 0.5h, and then extracted into dichloromethane and dried over $MgSO_4$. The solvent was evaporated and the residue purified by chromatography (Biotage Flash™, silica, 40g). Elution with cyclohexane / ethyl acetate (10:1) gave the title compound as a beige solid (74mg.).

LC/MS ESI R_T 4.62mins MH^+ 494

Intermediate 84

tert-Butyl 4-{[({[2-(4-thien-3-yl-1,3-thiazol-2-yl)phenyl]amino}carbonyl)oxy]methyl}piperidine-1-carboxylate

A mixture of tert-butyl 4-(hydroxymethyl)piperidine-1-carboxylate (CAS.123855-51-6;48mg) and diisopropylethylamine (50uL) in dry THF (1ml) was added dropwise to a solution of triphosgene (33mg) in dry THF (1ml) at 0-5°C under nitrogen. The mixture was stirred for 1 hr, then a solution of 2-(4-thien-3-yl-1,3-thiazol-2-yl)aniline (68mg) in THF (1ml) containing diisopropylethylamine (50uL) was added dropwise and the mixture stirred for 16 hr at room temperature. The mixture was treated with 4ml of

saturated sodium bicarbonate solution and 4ml of water, stirred for 0.5h, and then extracted into dichloromethane and dried over $MgSO_4$. The solvent was evaporated and the residue purified by chromatography (Biotage Flash™, silica, 40g). Elution with cyclohexane / ethyl acetate (10:1) gave the title compound as an off-white solid (101mg.).

LC/MS ESI R_T 4.59mins MH^+ 500.

Intermediate 85

tert-Butyl 4-{[({[2-(4-tert-butyl-1,3-thiazol-2-yl)phenyl]amino}carbonyl)oxy]methyl}piperidine-1-carboxylate

A mixture of tert-butyl 4-(hydroxymethyl)piperidine-1-carboxylate (CAS 123855-51-6; 48mg) and diisopropylethylamine (50uL) in dry THF (1ml) was added dropwise to a solution of triphosgene (33mg) in dry THF (1ml) at 0-5°C under nitrogen. The mixture was stirred for 1 hr, then a solution of 2-(4-tert-butyl-1,3-thiazol-2-yl)aniline (62mg) in THF (1ml) containing diisopropylethylamine (50uL) was added dropwise and the mixture stirred for 16 hr at room temperature. The mixture was treated with 4ml of saturated sodium bicarbonate solution and 4ml of water, stirred for 0.5h, and then extracted into dichloromethane and dried over $MgSO_4$. The solvent was evaporated and the residue purified by chromatography (Biotage Flash™, silica, 40g). Elution with cyclohexane / ethyl acetate (10:1) gave the title compound as a colourless oil (70mg).

LC/MS ESI R_T 4.54mins MH^+ 474.

Intermediate 86

tert-Butyl 4-{[({[2-(4,5-dimethyl-1,3-thiazol-2-yl)phenyl]amino}carbonyl)oxy]methyl}piperidine-1-carboxylate

A mixture of tert-butyl 4-(hydroxymethyl)piperidine-1-carboxylate (CAS No.123855-51-6; 48mg) and diisopropylethylamine (50uL) in dry THF (1ml) was added dropwise to a solution of triphosgene (33mg) in dry THF (1ml) at 0-5°C under nitrogen. The mixture was stirred for 1 hr, then a solution of 2-(4,5-dimethyl-1,3-thiazol-2-yl)aniline (54mg) in THF (1ml) containing diisopropylethylamine (50uL) was added dropwise and the mixture stirred for 16 hr at room temperature. The mixture was treated with 4ml of saturated sodium bicarbonate solution and 4ml of water, stirred for 0.5h, and then

extracted into dichloromethane and dried over $MgSO_4$. The solvent was evaporated and the residue purified by chromatography (Biotage Flash™, silica, 40g). Elution with cyclohexane / ethyl acetate (10:1) gave the title compound as a white solid (55mg). LC/MS ESI R_T 4.34mins MH^+ 446.

Intermediate 87

tert-Butyl 4-{[({[2-(4-ethyl -1,3-thiazol-2-yl)phenyl]amino}carbonyl)oxy]methyl}piperidine-1-carboxylate

A mixture of tert-butyl 4-(hydroxymethyl)piperidine-1-carboxylate (CAS 123855-51-6; 48mg) and diisopropylethylamine (50uL) in dry THF (1ml) was added dropwise to a solution of triphosgene (33mg) in dry THF (1ml) at 0-5°C under nitrogen. The mixture was stirred for 1 hr, then a solution of 2-(4-ethyl-1,3-thiazol-2-yl)aniline (49mg) in THF (1ml) containing diisopropylethylamine (50uL) was added dropwise and the mixture stirred for 16 hr at room temperature. The mixture was treated with 5ml of saturated sodium bicarbonate solution and 5 ml of water, stirred for 0.5h, and then extracted into dichloromethane and dried over $MgSO_4$. The solvent was evaporated and the residue purified by chromatography (Biotage Flash™, silica, 40g). Elution with ethyl acetate / cyclohexane (1:6) gave the title compound as a white solid (80mg). LC/MS ESI R_T 4.26mins MH^+ 446.

Intermediate 88

tert-Butyl 4-{[({[2-(5-methyl-1,3-thiazol-2-yl)phenyl]amino}carbonyl)oxy]methyl}piperidine-1-carboxylate

A mixture of tert-butyl 4-(hydroxymethyl)piperidine-1-carboxylate (CAS No.123855-51-6;72mg) and diisopropylethylamine (87uL) in dry THF (1ml) was added dropwise to a solution of triphosgene (50mg) in dry THF (2ml) at 0-5°C under nitrogen. The mixture was stirred for 1 hr, then a solution of 2-(5-methyl-1,3-thiazol-2-yl)aniline (64mg) in THF (2ml) containing diisopropylethylamine (87uL) was added dropwise and the mixture stirred for 16 hr at room temperature. The mixture was treated with 5ml of saturated sodium bicarbonate solution and 5 ml of water, stirred for 0.5h, and then extracted into dichloromethane and dried over MgSO4. The solvent was evaporated and

the residue purified by chromatography (Biotage Flash™, silica, 40g). Elution with ethyl acetate / cyclohexane (1:10) gave the title compound as a white solid (97mg). LC/MS ESI R_T 4.30mins MH^+ 432

Intermediate 89

tert-Butyl 4-{[({[2-(4-isopropyl-1,3-thiazol-2-yl)phenyl]amino}carbonyl)oxy]methyl}piperidine-1-carboxylate

A mixture of tert-butyl 4-(hydroxymethyl)piperidine-1-carboxylate (CAS 123855-51-6;48mg) and diisopropylethylamine (50ul) in dry THF (2ml) was added dropwise to a solution of triphosgene (33mg) in dry THF (2ml) at 0-5°C under nitrogen. The mixture was stirred for 1 hr, then a solution of 2-(4-isopropyl -1,3-thiazol-2-yl)aniline (49mg) in THF (2ml) containing diisopropylethylamine (50ul) was added dropwise and the mixture stirred for 16 hr at room temperature. The mixture was treated with 4ml of saturated sodium bicarbonate solution and 4 ml of water, stirred for 0.5h, and then extracted into dichloromethane and dried over $MgSO_4$. The solvent was evaporated and the residue purified by chromatography (Biotage Flash™, silica, 40g). Elution with cyclohexane / ethyl acetate (90:10) gave the title compound as a white solid (57mg.) LC/MS ESI R_T 4.39mins MH^+ 460.

Intermediate 90

tert-Butyl 4-({[({2-[4-(ethoxycarbonyl)-1,3-thiazol-2-yl]phenyl}amino)carbonyl]oxy}methyl)piperidine-1-carboxylate

Tert-butyl 4-(hydroxymethyl)piperidine-1-carboxylate (CAS-number 123855-51-6; 87mg) and diisopropylethylamine (74µL) in tetrahydrofuran (2ml) was added to a solution of triphosgene (39.7mg) in tetrahydrofuran (2ml) at 5°C over 2-3minutes. After stirring for 90 minutes a solution of ethyl 2-(2-aminophenyl)-1,3-thiazole-4-carboxylate (100mg) and diisopropylethylamine (74µL) in tetrahydrofuran (2ml) were added over 30 seconds at 5°C. The mixture was allowed to warm to 20°C and was stirred for a further 5 hours. The mixture was evaporated and purified using flash chromatography (SiO_2, hexane:ethyl acetate (6:1)) to give the title compound (132mg). NMR ($CDCl_3$, 400MHz, δ) 11.55 (1H,br s,NH) 8.50 (1H,d,aromatic CH) 8.14 (1H,s,aromatic CH) 7.73 (1H,dd,aromatic CH) 7.44 (dt,aromatic CH) 7.08

(1H,dt,aromatic CH) 4.43 (2H,q,CH_2) 4.13 (2H,br s, CH_2) 4.08 (2H,d,CH_2) 2.72 (2H,br t,CH_2) 1.91 (1H,m,CH) 1.82 (2H,br d,CH_2) 1.58 (3H,s,CH_3) 1.46 (9H,s,3CH_3) 1.43 3H,t,CH_3) 1.26 (2H,qd,CH_2)

Intermediate 91

tert-Butyl 4-({[({2-[4-(hydroxymethyl)-1,3-thiazol-2-yl]phenyl}amino)carbonyl]oxy}methyl)piperidine-1-carboxylate

A solution of diisopropylethylamine (133µl) and tert-butyl 4-(hydroxymethyl)piperidine-1-carboxylate (CAS-number 123855-51-6; 157.5mg) in tetrahydrofuran (3ml) was added to triphosgene (71.2mg) in tetrahydrofuran (3ml) at 3°C over 5 minutes. After 90 minutes a solution of 2-(2-aminophenyl)-4-(hydroxymethyl)-1,3-thiazole (149.6mg) and diisopropylethylamine (133µl) in tetrahydrofuran (3ml) was added to the cooled solution (0-5°C) over 5 minutes. The resultant solution was stirred at 0-5°C for a further 1 hour before allowing to warm to 20°C and stirring for 18 hours under nitrogen. The mixture was evaporated and partitioned between sodium carbonate (1M, 30ml) and ethyl acetate (3x30ml). The combined organics were washed with water (30ml) and the water back extracted with ethyl acetate (30ml). The combined organics were dried over magnesium sulphate and evaporated to yield the title compound (296mg).

NMR (DMSO, 400MHz, δ) 11.5 (1H,br,s,NH) 8.25 (1H,d,aromatic CH) 7.94 (1H,dd,aromatic CH) 7.63 (1H,s,aromatic CH) 7.53 (1H,td,aromatic CH) 7.24 (1H,td,aromatic CH) 4.70 (2H,s,CH_2) 4.06 (2H,d,CH_2) 4.01 (2H,b,m,CH_2) 2.78 (2H,m,CH_2) 1.90 (1H,m,CH) 1.73 (2H,br d,CH2) 1.45 (9H,s,3CH_3) 1.32 (1H,br dd, CH) 1.17 (2H, br qd, CH_2)

Intermediate 93

tert-Butyl 4-[({[(2-{4-[(methylamino)carbonyl]-1,3-thiazol-2-yl}phenyl)amino]carbonyl}oxy)methyl]piperidine-1-carboxylate

A solution of diisopropylethylamine (55µl) and tert-butyl 4-(hydroxymethyl)piperidine-1-carboxylate (CAS-number 123855-51-6; 65.3mg) in tetrahydrofuran (2ml) was added

to triphosgene (30mg) in tetrahydrofuran (2ml) at 0-5°C over 10 minutes. After 90 minutes a solution of 2-(2-aminophenyl)-N-methyl-1,3-thiazole-4-carboxamide (70.8mg) and diisopropylethylamine (55µl) in tetrahydrofuran (2ml) was added to the cooled solution (0-5°C) over 10 minutes. The resultant solution was stirred at 0-5°C for a further 1 hour before allowing to warm to 20°C and stirring for 3 days under nitrogen. The mixture was evaporated and partitioned between sodium carbonate (1M, 30ml) and ethyl acetate (3x30ml). The combined organics were washed with citric acid (0.5M, 30ml) which was back extracted with ethyl acetate (30ml). The combined organics were washed with sodium carbonate (1M, 20ml) which was back extracted with ethyl acetate (30ml). The combined organics were dried over magnesium sulphate, evaporated and purified using flash chromatography. Elution with hexane:ethyl acetate (2:1) gave the title compound (18mg).

NMR ($CDCl_3$, 400MHz, δ) 11.2 ((1H,br s,NH) 8.42 (1H,d,aromatic CH) 8.13 (1H,s,aromatic CH) 7.75 (1H,dd,aromatic CH) 7.47 (1H,dt,aromatic CH) 7.11 (dt,aromatic CH) 6.99 (1H,br d, NH) 4.16 (2H,m,CH_2) 4.10 (3H,br d,CH_3) 3.01 (2H,d,CH_2) 2.73 (2H,br t,CH_2) 1.88 (1H,m,CH) 1.76 (2H,br d,CH_2) 1.46 (9H,s,3CH_3)

Intermediate 94

Piperidin-4-ylmethyl 2-[4-(methoxymethyl)-1,3-thiazol-2-yl]phenylcarbamate trifluoroacetate

Tert-butyl 4-({[({2-[4-(methoxymethyl)-1,3-thiazol-2-yl]phenyl}amino)carbonyl]oxy}methyl)piperidine-1-carboxylate (8.5mg) was dissolved in trifluoroacetic acid (1ml) and water (0.1ml) added. The solution formed a suspension after 5 minutes, and was stirred for a further 90 minutes at 20°C before evaporating to dryness to yield the title compound (10.6mg).

NMR ($CDCl_3$, 400MHz, δ) 11.8 (1H,br s,NH) 9.05 (1H,br s, NH^+) 8.39 (1H,d,aromatic CH) 8.32 (1H,br s, NH^+) 7.74 (1H,dd,aromatic CH), 7.41 (dt,aromatic CH) 7.23 (1H,s,aromatic CH)) 7.09 (1H,dt,aromatic CH) 4.64 (2H,s,CH_2) 4.12 (2H,d,CH_2) 3.52 (2H,br d,CH_2) 3.48 (3H,s,CH_3) 2.99 (2H,br q,CH_2) 2.05 (3H,br d,CH_3) 1.69 (2H,br q,CH_2)

Intermediate 95

tert-Butyl 4-{[({[2-(4-propyl-1,3-thiazol-2-yl)phenyl]amino}carbonyl)oxy]methyl}piperidine-1-carboxylate

A mixture of tert-butyl 4-(hydroxymethyl)piperidine-1-carboxylate (680mg) and diisopropylethylamine (1.65ml) in dry THF (10ml) was added dropwise to a solution of triphosgene (284mg) in dry THF (5ml) at 0-5°C under nitrogen. The mixture was stirred for 3h, then a solution of 2-(4-propyl-1,3-thiazol-2-yl)aniline (626mg) in dry THF(5ml) was added dropwise and the mixture stirred for 16h at room temperature. Water (10ml) followed by ethyl acetate 10ml) were added to the reaction. The aqueous phase was extracted with ethyl acetate (10ml). The combined organics were washed with brine (15ml) and dried ($MgSO_4$). The solvent was evaporated and the residue purified by Varian Mega Bond Elut®; on silica. Elution with 10% dichloromethane / cyclohexane followed with 10% ethyl acetate gave the title compound as a white solid (1.068g)

LC/MS ESI R_T 4.40mins MH^+ 460

Tlc SiO_2 (Cyclohexane / Ethyl acetate 1:8) R_f 0.19

Intermediate 96

tert-Butyl 4-{[({[2-(4-pentyl-1,3-thiazol-2-yl)phenyl]amino}carbonyl)oxy]methyl}piperidine-1-carboxylate

And

tert-butyl 4-{[({[2-(5-butyl –4-methyl-1,3-thiazol-2-yl)phenyl]amino}carbonyl)oxy]methyl}piperidine-1-carboxylate

A mixture of tert-butyl 4-(hydroxymethyl)piperidine-1-carboxylate (723mg) and diisopropylethylamine (1.75ml) in dry THF (10ml) was added dropwise to a solution of triphosgene (302mg) in dry THF (5ml) at 0-5°C under nitrogen. The mixture was stirred for 1.5h, then a solution of a mixture of 2-(4-pentyl-1,3-thiazol-2-yl)aniline and 2-(5-butyl- 4- methyl-1,3-thiazol-2-yl)aniline (760mg) in dry THF(5ml) was added dropwise. The mixture was stirred for 7days at room temperature. Water (10ml) followed by ethyl acetate (10ml) were added to the reaction. The aqueous phase was extracted with ethyl acetate (10ml). The combined organics were washed with brine (20ml) and dried (Na_2SO_4). The solvent was evaporated and the residue purified by

flash column chromatography on silica. Elution with cyclohexane / ethyl acetate 8:1 afforded the title compounds as a yellow oil (1.1g)

LC/MS ESI R_T 4.65mins MH^+ 488

LC/MS ESI R_T 4.52mins MH^+ 488

Tlc SiO_2 (Cyclohexane / Ethyl acetate 8;1) Rf 0.16

Intermediate 97

tert-Butyl 4-{[({[2-(4-butyl-1,3-thiazol-2-yl) phenyl]amino}carbonyl)oxy]methyl}piperidine-1-carboxylate

A mixture of tert-butyl 4-(hydroxymethyl)piperidine-1-carboxylate (690mg) and diisopropylethylamine (1.5ml) in dry THF (10ml) was added dropwise to a solution of triphosgene (288mg) in dry THF (5ml) at 0-5°C under nitrogen. The mixture was stirred for 3h, then a solution of 2-(4-butyl-1,3-thiazol-2-yl)aniline (677mg) in dry THF(5ml) was added dropwise. The mixture was stirred for 16h at room temperature. Water (10ml) followed with ethyl acetate (10ml) were added to the reaction. The aqueous phase was extracted with ethyl acetate (10ml). The combined organics were washed with brine (10ml) and dried (Na_2SO_4). The solvent was evaporated and the residue purified by Biotage Flash™ on silica. Elution with dichloromethane followed by ethylacetate gave the title compound as a pale yellow powder (660mg)

LC/MS ESI R_T 4.11mins MH^+ 474

Tlc SiO_2 (Dichloromethane) Rf 0.1

Intermediate 98

tert-Butyl 4-[({[(2-{4-methyl-5-[(methylamino)carbonyl]-1,3-thiazol-2-yl}phenyl)amino]carbonyl}oxy)methyl]piperidine-1-carboxylate

A mixture of tert-butyl 4-(hydroxymethyl)piperidine-1-carboxylate (43mg) and diisopropylethylamine (0.095ml) in dry THF (3ml) was added dropwise to a solution of triphosgene (16mg) in dry THF (5ml) at 0-5°C under nitrogen. The mixture was stirred for 3h, then a solution of 2-(2-aminophenyl)-N,4-dimethyl-1,3-thiazole-5-carboxamide (45mg) in dry THF(35ml) was added dropwise. The mixture was stirred for 16h at room temperature. Water (5ml) followed with ethyl acetate (8ml) were added to the reaction. The aqueous phase was extracted with ethyl acetate (8ml). The combined

organics were washed with brine (10ml) and dried (Na_2SO_4). The solvent was evaporated and the residue purified by using a Varian Mega Bond Elut® 10g silica solid phase extraction cartridge with 1:1 ethyl acetate / cyclohexane as the eluent. The material was re-purified by Biotage Flash™, on silica. Elution with 1:1 cyclohexane / ethyl acetate gave the title compound as a yellow oil (50mg)

LC/MS ESI R_T 3.81mins MH^- 487

Tlc SiO_2 (cyclohexane / ethyl acetate, 1:1) R_f 0.23

Intermediate 99

tert-Butyl 4-[({[(2-{4-[2-(benzyloxy)ethyl]-1,3-thiazol-2-yl}phenyl)amino]carbonyl}oxy)methyl]piperidine-1-carboxylate

Diisopropylethylamine (0.57ml) was added to a solution of triphosgene (320mg) in dry THF (2.5ml) at 0-5°C under nitrogen. After stirring for 2 minutes, a solution of tert-butyl 4-(hydroxymethyl)piperidine-1-carboxylate (694mg) in dry THF (3ml) was added and the resulting mixture was stirred for 2 hours 30mins at 0-5°C. A solution of 2-{4-[2-(benzyloxy)ethyl]-1,3-thiazol-2-yl}aniline (1g) in dry THF (7ml) and diisopropylethylamine (0.57ml) were then successively added. The mixture thus obtained was stirred for 16 hours at room temperature then partitioned between ethyl acetate (200ml) and saturated aqueous sodium bicarbonate (150ml). The aqueous layer was separated, extracted with ethyl acetate (100ml). The organic extracts were combined, dried ($MgSO_4$) and evaporated. The resulting residue was purified by flash column chromatography. Elution with hexane/ethyl acetate 4:1 gave the title compound as a pale yellow solid (1.27g).

LC/MS ESI R_T 4.47mins MH^+ 552.3

Tlc SiO_2 (Hexane / Ethyl acetate 4:1) R_f 0.18

Intermediate 100

tert-Butyl 4-{[({[2-(4-formyl-1,3-thiazol-2-yl)phenyl]amino}carbonyl)oxy]methyl}piperidine-1-carboxylate

To a solution of oxalyl chloride (0.136ml) in dichloromethane (1ml) was added DMSO (0.259ml) at –78°C. After stirring for one hour at that temperature, a solution of tert-butyl 4-({[({2-[4-(hydroxymethyl)-1,3-thiazol-2-

yl]phenyl}amino)carbonyl]oxy}methyl)piperidine-1-carboxylate (465mg) in dichloromethane (4ml) was added dropwise. Thirty minutes later, triethylamine (1 ml) was added and the resulting solution was stirred for one hour at –78°C then allowed to warm-up slowly to room temperature. The reaction mixture was partitioned between dichloromethane (50ml) and water (20ml). The organic layer was separated, washed with 0.5 M hydrochloric acid (20ml) then saturated aqueous sodium bicarbonate (20ml) before drying ($MgSO_4$). After evaporation, the title compound was obtained as a white solid (450mg).

LC/MS ESI R_T 3.78mins MH^+ 446.5

Tlc SiO_2 (Hexane / Ethyl acetate 1:1) R_f 0.44

Intermediate 101

tert-Butyl 4-({[({2-[4-(difluoromethyl)-1,3-thiazol-2-yl]phenyl}amino)carbonyl]oxy}methyl)piperidine-1-carboxylate

To a solution of tert-butyl 4-{[({[2-(4-formyl-1,3-thiazol-2-yl)phenyl]amino}carbonyl)oxy]methyl}piperidine-1-carboxylate (150mg) in dichloromethane (0.5ml) was added (diethylamino)sulfur trifluoride (0.065ml) at 0°C. After stirring at room temperature for 18 hours, the reaction mixture was partitioned between dichloromethane (40ml) and water (10ml). The aqueous phase was separated and extracted with dichloromethane (10ml). The combined organic extracts were washed with saturated aqueous sodium bicarbonate (20ml), dried ($MgSO_4$) and evaporated to give a crude material which was purified by flash chromatography. Elution with ethyl acetate/hexane 3:1 gave the title compound as a white solid (85mg).

LC/MS ESI R_T 3.93mins MH^+ 467.5

Tlc SiO_2 (Hexane / Ethyl acetate 1:1) R_f 0.57

Intermediate 102

tert-Butyl 4-({[({2-[4-(fluoromethyl)-1,3-thiazol-2-yl]phenyl}amino)carbonyl]oxy}methyl)piperidine-1-carboxylate

To a solution of 4-({[({2-[4-(hydroxymethyl)-1,3-thiazol-2-yl]phenyl}amino)carbonyl]oxy}methyl)piperidine-1-carboxylate (150mg) in dichloromethane (0.5ml) was added (diethylamino)sulfur trifluoride (0.046ml) at 0°C.

After stirring at room temperature for 3 hours 20 mins, more (diethylamino)sulfur trifluoride (0.015ml) was added. After stirring for another 16 hours, the reaction mixture was partitioned between dichloromethane (40ml) and water (10ml). The aqueous phase was separated and extracted with dichloromethane (10ml). The combined organic extracts were washed with saturated aqueous sodium bicarbonate (20ml), dried ($MgSO_4$) and evaporated to give a crude material which was purified by flash chromatography. Elution with ethyl acetate/hexane 3:1 gave the title compound as a white solid (47mg).

LC/MS ESI R_T 3.90mins MH^+ 450.0

Tlc SiO_2 (Hexane / Ethyl acetate 1:1) R_f 0.55

Intermediate 103

tert-Butyl 4-({[({2-[4-(1-hydroxyethyl)-1,3-thiazol-2-yl]phenyl}amino)carbonyl]oxy}methyl)piperidine-1-carboxylate

To a solution of tert-butyl 4-{[({[2-(4-formyl-1,3-thiazol-2-yl)phenyl]amino}carbonyl)oxy]methyl}piperidine-1-carboxylate (150mg) in THF (3ml) at –78°C was added a 3N solution of methyl magnesium chloride in THF (0.27ml). The resulting solution was stirred and allowed to warm up to room temperature over 16 hours. After quenching with water (1ml), the mixture was partitioned between with dichloromethane (200ml) and water (50ml). The organic phase was separated, washed with saturated aqueous sodium bicarbonate, dried ($MgSO_4$) and evaporated to give the tile compound as a pale yellow solid (135mg).

LC/MS ESI R_T 3.77mins MH^+ 462.6

Tlc SiO_2 (Hexane / Ethyl acetate 1:1) R_f 0.34

Intermediate 104

(*R*)-tert-Butyl 4-({[({2-[4-(1-hydroxyethyl)-1,3-thiazol-2-yl]phenyl}amino)carbonyl]oxy}methyl)piperidine-1-carboxylate

Diisopropylethylamine (0.23ml) was added to a solution of triphosgene (128mg) in dry THF (3ml) at 0-5°C under nitrogen. After stirring for 10 minutes, a solution of tert-butyl 4-(hydroxymethyl)piperidine-1-carboxylate (282mg) in dry THF (5ml) was added and the resulting mixture was stirred for 1 hour at 0-5°C. A solution of (*R*)-2-[4-(1-hydroxyethyl)-1,3-thiazole-2-yl]aniline (330mg) in dry THF (5ml) and

diisopropylethylamine (0.23ml) were then successively added. The mixture thus obtained was stirred for 16 hours at room temperature then partitioned between ethyl acetate (150ml) and water (50ml). The aqueous layer was separated and extracted with ethyl acetate (100ml). The organic extracts were combined, washed with saturated aqueous sodium bicarbonate (20ml), dried ($MgSO_4$) and evaporated to give a residue which was purified by flash column chromatography. Elution with hexane/ethyl acetate 3:1 gave the title compound as white solid (475mg).

LC/MS ESI R_T 3.87mins MH^+ 462.6

Tlc SiO_2 (Hexane/Ethyl acetate 1:1) R_f 0.34

Intermediate 105

tert-Butyl 4-{[({[2-(4-acetyl-1,3-thiazol-2-yl)phenyl]amino}carbonyl)oxy]methyl}piperidine-1-carboxylate

To a solution of oxalyl chloride (0.024ml) in dichloromethane (2ml) was added DMSO (0.041ml) at –78°C. After stirring for one hour at that temperature, a solution of tert-butyl 4-({[({2-[4-(1-hydroxyethyl)-1,3-thiazol-2-yl]phenyl}amino)carbonyl]oxy}methyl)piperidine-1-carboxylate (83mg) in dichloromethane (1.5ml) was added dropwise. Fifteen minutes later, triethylamine (0.18 ml) was added and the resulting solution was stirred for one hour at –78°C then allowed to warm-up slowly to room temperature over 3 hours. The reaction mixture was partitioned between dichloromethane (50ml) and water (20ml). The organic layer was separated, washed with 0.5 M hydrochloric acid (20ml) and saturated aqueous sodium bicarbonate (20ml) then dried ($MgSO_4$). After evaporation, the title compound was obtained as a white solid (85mg).

LC/MS ESI R_T 3.92mins MH^+ 460.6

Tlc SiO_2 (Hexane / Ethyl acetate 1:1) R_f 0.58

Intermediate 106

tert-Butyl 4-({[({2-[4-(1,1-difluoroethyl)-1,3-thiazol-2-yl]phenyl}amino)carbonyl]oxy}methyl)piperidine-1-carboxylate

To a solution of tert-butyl 4-{[({[2-(4-acetyl-1,3-thiazol-2-yl)phenyl]amino}carbonyl)oxy]methyl}piperidine-1-carboxylate (81mg) in dichloromethane (1ml) was added diethyl amino sulfur trifluoride (0.45ml). After stirring at room temperature for 24 hours, more diethyl amino sulfur trifluoride (0.45ml) was added. After stirring for a further 4 days, the reaction mixture was partitioned between dichloromethane (50ml) and water (10ml). The aqueous phase was separated and extracted with dichloromethane (20ml). The combined organic extracts were washed with saturated aqueous sodium bicarbonate (20ml), dried ($MgSO_4$) and evaporated to give a crude material which was purified by flash chromatography. Elution with ethyl acetate/hexane 4?3:1 gave the title compound as a pale yellow solid (40mg).

LC/MS ESI R_T 4.11mins MH^+ 480.2

Intermediate 107

tert-Butyl 4-({[({2-[4-(2-ethoxy-2-oxoethyl)-1,3-thiazol-2-yl]phenyl}amino)carbonyl]oxy}methyl)piperidine-1-carboxylate

Diisopropylethylamine (0.57ml) was added to a solution of triphosgene (320mg) in dry THF (2.5ml) at 0-5°C under nitrogen. After stirring for 2 minutes, a solution of tert-butyl 4-(hydroxymethyl)piperidine-1-carboxylate (698mg) in dry THF (6ml) was added and the resulting mixture was stirred for 1 hour at 0-5°C. A solution of ethyl [2-(2-aminophenyl)-1,3-thiazol-4-yl]acetate (0.85g) in dry THF (5ml) and diisopropylethylamine (0.57ml) were then successively added. The mixture thus obtained was stirred for 16 hours at room temperature then partitioned between ethyl acetate (200ml) and saturated aqueous sodium bicarbonate (150ml). The aqueous layer was separated and extracted with ethyl acetate (100ml). The organic extracts were combined, dried ($MgSO_4$) and evaporated to give a residue which was purified by flash column chromatography. Elution with hexane / ethyl acetate 4:1 gave the title compound as pale yellow solid (0.92g).

LC/MS ESI R_T 4.12mins MH^+ 504.3

Tlc SiO_2 (Hexane/Ethyl acetate 4:1) R_f 0.11

Intermediate 108

tert-Butyl 4-({[({2-[4-(2-hydroxyethyl)-1,3-thiazol-2-yl]phenyl}amino)carbonyl]oxy}methyl)piperidine-1-carboxylate

To solution of tert-butyl 4-({[({2-[4-(2-ethoxy-2-oxoethyl)-1,3-thiazol-2-yl]phenyl}amino)carbonyl]oxy}methyl)piperidine-1-carboxylate (822mg) in THF (10ml) was added lithium borohydride (35mg). After stirring at room temperature for 6 hours, more lithium borohydride (35mg) was added and the resulting mixture was stirred at room temperature for 15 hours. Methanol (10ml) was then added and the mixture was stirred for 10 mins. The solvents were evaporated and the residue was partitioned between ethyl acetate (150ml) and water (50ml). The aqueous phase was separated and extracted with ethyl acetate (50ml). The organic extracts were combined, dried ($MgSO_4$) and evaporated to a pale yellow solid (765mg). A portion of this solid (610mg) was purified by flash column chromatography. Elution with ethyl acetate/cyclohexane 1:1 afforded the title compound as white solid (515mg).

LC/MS ESI R_T 3.84mins MH^+ 462.2

Intermediate 109

tert-Butyl 4-({[({2-[4-(2-fluoroethyl)-1,3-thiazol-2-yl]phenyl}amino)carbonyl]oxy}methyl)piperidine-1-carboxylate

To solution of tert-butyl 4-({[({2-[4-(2-hydroxyethyl)-1,3-thiazol-2-yl]phenyl}amino)carbonyl]oxy}methyl)piperidine-1-carboxylate (68mg) in dichloromethane(0.5ml) was added (diethylamino)sulphur trifluoride (0.40ml). After stirring for 6 hours and 10mins at room temperature, more (diethylamino)sulphur trifluoride (0.40ml) and dichloromethane (0.5ml) were added. The resulting solution was stirred at room temperature for 21 hours. The mixture was diluted with dichloromethane (100ml) and washed with aqueous saturated sodium bicarbonate (50ml). The aqueous phase was separated and extracted with dichloromethane (100ml). The organic extracts were combined, dried ($MgSO_4$) and evaporated to give a crude oil which was purified by flash column chromatography. Elution with ethyl acetate/cyclohexane 4:1 afforded the title compound as a pale yellow solid (57mg).

LC/MS ESI R_T 4.15mins MH^+ 464.2

Tlc SiO_2 (Hexane/Ethyl acetate 4:1) Rf 0.20

Intermediate 110

tert-Butyl 4-({[({2-[4-(2,2-difluoroethyl)-1,3-thiazol-2-yl]phenyl}amino)carbonyl]oxy}methyl)piperidine-1-carboxylate

Diisopropylethylamine (0.034ml) was added to a solution of triphosgene (19mg) in dry THF (0.2ml) at 0-5°C. After stirring for 5 minutes, a solution of tert-butyl 4-(hydroxymethyl)piperidine-1-carboxylate (41.1mg) in dry THF (0.5ml) was added and the resulting mixture was stirred for 1 hour 25 mins. A solution of 2-[4-(2,2-difluoroethyl)-1,3-thiazol-2-yl]aniline in THF (0.5ml) and diisopropylethylamine (0.034ml) were successively added and the mixture thus obtained was stirred for 16 hours from 0°C to room temperature. The reaction mixture was then partitioned between ethyl acetate (30ml) and saturated aqueous sodium bicarbonate (20ml). The aqueous phase was separated and extracted with ethyl acetate (20ml). The organic extracts were combined, dried ($MgSO_4$) and evaporated. The crude residue was purified by flash chromatography. Elution with ethyl acetate/cyclohexane 1:3 gave the title compound (42mg).

LC/MS ESI R_T 4.20mins MH^+ 482.5

Intermediate 111

tert-Butyl 4-{[({[2-(4-cyclobutyl-1,3-thiazol-2-yl)phenyl]amino}carbonyl)oxy]methyl}piperidine-1-carboxylate

A solution of tert-butyl 4-(hydroxymethyl)piperidine-1-carboxylate (CAS-number 123855-51-6, 176mg) and N,N-diisopropylethylamine (439µl) in dry tetrahydrofuran (3ml) was added dropwise to a cooled (0°C) solution of triphosgene (122mg) in dry tetrahydrofuran (7ml) under an atmosphere of nitrogen. The resulting solution was stirred at room temperature for 1.5h and then cooled to 0°C once more. A solution of 2-(4-cyclobutyl-1,3-thiazol-2-yl)aniline (188mg) in dry tetrahydrofuran (1ml) was added and the mixture was stirred at room temperature for 16h. Water was added and after 4hr the mixture was extracted with ethyl acetate. The combined organic extracts were washed with brine and dried (Na_2SO_4). The solvent was removed and the residue was purified by column chromatography on silica. Elution with cyclohexane / ethyl acetate 8:1 gave the title compound as a yellow oil which solidified on standing (285mg).

LC/MS ESI R_T 4.56mins MH^+ 472

Intermediate 112

tert-Butyl 4-{[({[2-(4-cyclohexyl-1,3-thiazol-2-yl)phenyl]amino}carbonyl)oxy]methyl}piperidine-1-carboxylate

A solution of 2-(4-cyclohexyl-1,3-thiazol-2-yl)aniline (155mg) and N,N-diisopropylethylamine (314µl) in dry tetrahydrofuran (2ml) was added dropwise to a cold (0°C) solution of triphosgene (94mg) in tetrahydrofuran (5ml) under an atmosphere of nitrogen and the solution was stirred at 0°C for 10mins. A solution of tert-butyl 4-(hydroxymethyl)piperidine-1-carboxylate (CAS-number 123855-51-6, 129mg) in dry tetrahydrofuran (1ml) was added and the resulting solution was heated at 70°C for 3 days. Sodium bicarbonate (8%) / water 1:1 and dichloromethane were added and the resulting mixture was stirred vigorously for 1.5h. The reaction mixture was partitioned between the two phases and the combined organic extracts were washed with brine and dried (Na_2SO_4). The solvent was removed and the residue was purified by column chromatography on silica using cyclohexane / ethyl acetate (9:1) as eluant. This gave the title compound (63mg).

LC/MS ESI R_T 4.75mins MH^+ 500

Intermediate 113

tert-Butyl 4-{[({[2-(4-cyclopentyl-1,3-thiazol-2-yl)phenyl]amino}carbonyl)oxy]methyl}piperidine-1-carboxylate

A solution of tert-butyl 4-(hydroxymethyl)piperidine-1-carboxylate (CAS-number 123855-51-6, 54mg) and N,N-diisopropylethylamine (130µl) in dry tetrahydrofuran (2ml) was added dropwise to a cooled (0°C) solution of triphosgene (38mg) in dry tetrahydrofuran (4ml) under an atmosphere of nitrogen. The resulting solution was stirred at room temperature for 1.5h and then cooled to 0°C once more. A solution of 2-(4-cyclopentyl-1,3-thiazol-2-yl)aniline (60mg) in dry tetrahydrofuran (1ml) was added and the mixture was stirred at room temperature for 3 days. Sodium bicarbonate (8%) / water 1:1 was added and after 1.5hr the mixture was extracted with dichloromethane. The combined organic extracts were washed with brine and dried (Na_2SO_4). The solvent was evaporated and the residue was purified by column

chromatography on silica. Elution with cyclohexane / ethyl acetate 9:1 gave the title compound as a white solid (26mg).

LC/MS ESI R_T 4.79mins MH^+ 486

Intermediate 114

tert-Butyl 4-({[({2-[4-(cyclopropylmethyl)-1,3-thiazol-2-yl]phenyl}amino)carbonyl]oxy}methyl)piperidine-1-carboxylate

A mixture of tert-butyl 4-(hydroxymethyl)piperidine-1-carboxylate (CAS-number 123855-51-6; 231mg) and diisopropylethylamine (0.375ml) in dry THF (7.5ml) was added dropwise to a solution of triphosgene (160mg) in dry THF (7.5ml) at 0-5°C under nitrogen . The mixture was stirred for 1h at room temperature, re-cooled to 0-5°C, then a solution of 2-[4-(cyclopropylmethyl)-1,3-thiazol-2-yl]aniline (248mg) in dry THF (7.5ml) containing diisopropylethylamine (0.187ml) was added dropwise and the mixture stirred for 18h at room temperature. The reaction was treated with saturated aqueous sodium bicarbonate solution (30ml) and extracted with dichloromethane (x3). Combined organics were washed with brine, dried over anhydrous magnesium sulphate, filtered and evaporated in vacuo. The residue was purified by Varian Mega Bond Elut® (Si, 10g); elution with 0-65% dichloromethane in cyclohexane followed by 100% dichloromethane gave the title compound as a white solid (162mg).

LC/MS ESI R_T 4.55mins MH^+ 472

Intermediate 115

tert-Butyl 4-{[({[2-(4-isobutyl-1,3-thiazol-2-yl)phenyl]amino}carbonyl)oxy]methyl}piperidine-1-carboxylate

A mixture of tert-butyl 4-(hydroxymethyl)piperidine-1-carboxylate (CAS-number 123855-51-6; 187mg) and diisopropylethylamine (0.304ml) in dry THF (6ml) was added dropwise to a solution of triphosgene (130mg) in dry THF (6ml) at 0-5°C under nitrogen . The mixture was stirred for 1h at room temperature, re-cooled to 0-5°C, then a solution of 2-(4-isobutyl-1,3-thiazol-2-yl)aniline (203mg) in dry THF (6ml) containing diisopropylethylamine (0.152ml) was added dropwise and the mixture stirred for 72h at room temperature. The reaction was treated with saturated aqueous sodium bicarbonate solution (30ml) and extracted with dichloromethane (x3).

Combined organics were washed with brine, dried over anhydrous magnesium sulphate, filtered and evaporated in vacuo. The oil was purified by Varian Mega Bond Elut® (Si, 10g); elution with 0-65% dichloromethane in cyclohexane followed by 100% dichloromethane gave the title compound as a white solid (148mg).

LC/MS ESI R_T 4.69mins MH^+ 474

Intermediate 116

tert-Butyl 2-{2-[({[1-(tert-butoxycarbonyl)piperidin-4-yl]methoxy}carbonyl)amino]phenyl}-6,7-dihydro[1,3]thiazolo[5,4-c]pyridine-5(4H)-carboxylate

A mixture of tert-butyl 4-(hydroxymethyl)piperidine-1-carboxylate (CAS-number 123855-51-6; 26.6mg) and diisopropylethylamine (0.043ml) in dry THF (1ml) was added dropwise to a solution of triphosgene (18.5mg) in dry THF (1ml) at 0-5°C under nitrogen . The mixture was stirred for 1h at room temperature, re-cooled to 0-5°C, then a solution of tert-butyl 2-(2-aminophenyl)-6,7-dihydro[1,3]thiazolo[5,4-c]pyridine-5(4H)-carboxylate (41mg) in dry THF (2ml) containing diisopropylethylamine (0.022ml) was added dropwise and the mixture stirred for 20h at room temperature. The reaction was treated with saturated aqueous sodium bicarbonate solution and extracted with dichloromethane (x2). Combined organics were washed with brine, dried over anhydrous magnesium sulphate, filtered and evaporated in vacuo. The residue was purified by Varian Mega Bond Elut® (Si, 1g); elution with 0-90% dichloromethane in cyclohexane gave the title compound as a light yellow residue (27mg)

LC/MS ESI R_T 4.56min MH^+ 573

Intermediate 117

tert-Butyl 4-{[({[2-(5,6-dihydro-4H-cyclopenta[d][1,3]thiazol-2-yl)phenyl]amino}carbonyl)oxy]methyl}piperidine-1-carboxylate

A mixture of tert-butyl 4-(hydroxymethyl)piperidine-1-carboxylate (CAS-number 123855-51-6; 104mg) and diisopropylethylamine (0.168ml) in dry THF (5ml) was added dropwise to a solution of triphosgene (72mg) in dry THF (5ml) at 0-5°C under nitrogen . The mixture was stirred for 1h at room temperature, re-cooled to 0-5°C, then a solution of 2-(5,6-dihydro-4H-cyclopenta[d][1,3]thiazol-2-yl)aniline (104mg) in dry THF (5ml) containing diisopropylethylamine (0.084ml) was added dropwise and the mixture stirred for 20h at room temperature. The reaction was treated with saturated aqueous sodium bicarbonate solution and extracted with dichloromethane (x2). Combined organics were washed with brine, dried over anhydrous magnesium sulphate, filtered and evaporated in vacuo. The residue was purified by Varian Mega

Bond Elut® (Si, 5g); elution with 0-90% dichloromethane in cyclohexane gave the title compound as a light yellow solid (162mg).
LC/MS ESI R_T 4.55mins MH^+ 458

Intermediate 118

tert-Butyl 4-[({[(2-bromophenyl)amino]carbonyl}oxy)methyl]piperidine-1-carboxylate

A solution of tert-butyl 4-(hydroxymethyl)piperidine-1-carboxylate (CAS-number 123855-51-6, 2.5g) in dry tetrahydrofuran (10ml) was added dropwise to a cooled (0°C) solution of triphosgene (1.69g) in dry tetrahydrofuran (80ml) under an atmosphere of nitrogen. N,N-diisopropylethylamine (3ml) was added dropwise and the resulting solution was stirred at room temperature for 1.5h and then cooled to 0°C once more. A solution of o-bromoaniline (2g) and N,N-diisopropylethylamine (3ml) in dry tetrahydrofuran (10ml) was added and the mixture was stirred at room temperature for 3 days. Water was added followed by sodium bicarbonate (8%) and after 1hr the mixture was extracted with dichloromethane. The combined organic extracts were washed with brine and dried (Na_2SO_4). The solvent was removed and the residue was purified by column chromatography on silica. Elution with cyclohexane / ethyl acetate 10:1 gave the title compound (2.3g)
LC/MS ESI R_T 3.80mins MH^+ 413,415

Intermediate 119

tert-Butyl 4-{[({[2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]amino}carbonyl)oxy]methyl}piperidine-1-carboxylate

A solution of bis(pinacolato)diboron (623mg) in dry dimethoxyethane (2ml) was added to a solution of tert-butyl 4-[({[(2-bromophenyl)amino]carbonyl}oxy)methyl]piperidine-1-carboxylate. Potassium acetate (602mg) and 1,1'-bis(diphenylphosphino)ferrocene-palladium dichloride (167mg) were added and the resulting mixture was heated at 80°C for 16h. The mixture was partitioned between brine and dichloromethane and the combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to give a brown oil. This residue was purified (Varian Mega Bond Elut®) using cyclohexane / ethyl acetate 7:1 as eluant to give the title compound as a colourless oil (454mg).

LC/MS ESI R_T 4.21mins MH^+ 461

Intermediate 120

tert-Butyl 4-{[({[2-(1,3-thiazol-2-yl)phenyl]amino}carbonyl)oxy]methyl}piperidine-1-carboxylate

2-Bromothiazole (0.59ml) was added to a solution of tert-butyl 4-{[({[2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]amino}carbonyl)oxy]methyl}piperidine-1-carboxylate (1.0g) in dry dimethoxyethane (20ml, pretreated with activated alumina). Triethylamine (0.92ml) was added followed by tetrakis(triphenylphosphino)palladium (0) (254mg) and water (2ml). The resulting reaction mixture was heated at 88°C for 16h. After cooling the reaction was concentrated *in vacuo* and the residue was partitioned between brine and ethyl acetate. The combined organic extracts were dried (Na_2SO_4) and the solvent was removed to give an oil which was purified by column chromatography on silica. Elution with cyclohexane / ethyl acetate (6:1) gave the title compound as a colourless oil (120mg).

LC/MS ESI R_T 4.17mins MH^+ 418

Bromo Intermediate

tert-Butyl 4-{[({[2-(4-bromo-1,3-thiazol-2-yl)phenyl]amino}carbonyl)oxy]methyl}piperidine-1-carboxylate

2,4-Dibromothiazole (CAS-number 4175-77-3, 150 mg) was added to a solution of tert-butyl 4-{[({[2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]amino}carbonyl)oxy]methyl}piperidine-1-carboxylate (251 mg) in dry dimethoxyethane (10ml). A 2 N aqueous solution of sodium carbonate (1.8 ml) was added and a flow of nitrogen was bubbled through the reaction mixture for 15 mins. Tetrakis(triphenylphosphino)palladium (0) (143 mg) was added and the resulting reaction mixture was heated at 88°C for 16h. After cooling the reaction was partitioned between ethyl acetate (150 ml) and water (30 ml). The organic layer was separated, dried (Na_2SO_4) and the solvent was removed to give an oil which was purified by column chromatography on silica. Elution with cyclohexane / ethyl acetate (9:1) gave the title compound as a colorless oil (101 mg).

LC/MS ESI R_T 4.25mins MH^+ 496, $M+2H^+$ 498

Chloro Intermediate

tert-Butyl 4-{[({[2-(4-chloro-1,3-thiazol-2-yl)phenyl]amino}carbonyl)oxy]methyl}piperidine-1-carboxylate

2,4-Dichlorothiazole (CAS-number 4175-76-2, 114 mg) was added to a solution of tert-butyl 4-{[({[2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]amino}carbonyl)oxy]methyl}piperidine-1-carboxylate (300 mg) in dry dimethoxyethane (12 ml). A 2 N aqueous solution of sodium carbonate (2.2 ml) was added and a flow of nitrogen was bubbled through the reaction mixture for 15 mins. Tetrakis(triphenylphosphino)palladium (0) (170 mg) was added and the resulting reaction mixture was heated at 88°C for 16h. After cooling the reaction was partitioned between ethyl acetate (150 ml) and water (50 ml). The organic layer was separated, dried ($MgSO_4$) and the solvent was removed to give an oil which was purified by column chromatography on silica. Elution with cyclohexane / ethyl acetate (4:1) gave the title compound as a colorless oil (150 mg).

LC/MS ESI R_T 4.16mins MH^+ 452.

Intermediate 125

Benzyl 4-fluoro-4-[2-({[2-(4-methyl-1,3-thiazol-2-yl)phenyl]amino}oxy)-2-oxoethyl]piperidine-1-carboxylate

Triphosgene (39mg) was added in one portion to a solution of 1-Piperidinecarboxylic acid, 4-fluoro-4-(hydroxymethyl)-, phenylmethyl ester (CAS 240400-84-4)(70mg) and diisopropylethylamine (68mg) in dry THF(5ml) at 0°C under nitrogen. The mixture was allowed to warm to room temperature and stirred for 1h. 2-(4-methyl-1,3-thiazol-2-yl)aniline (50mg) was added in one portion and the mixture stirred for 16h, then partitioned between water (10ml) and ethyl acetate (3x10ml). The combined organic extracts were washed with brine (10ml) and dried ($MgSO_4$). The solvent was evaporated and the residue purified by chromatography on silica. Elution with hexane / ethyl acetate 3:1 gave the title compound as a colourless oil (101mg)

Tlc SiO_2 (Hexane / ethyl acetate 3:1) R_f 0.2.

Intermediate 126

tert-Butyl (2R,6R)-2,6-dimethyl-4-{[({[2-(4-methyl-1,3-thiazol-2-yl)phenyl]amino}carbonyl)oxy]methyl}piperidine-1-carboxylate isomer 1(A)
and
tert-butyl (2S,6S)-2,6-dimethyl-4-{[({[2-(4-methyl-1,3-thiazol-2-yl)phenyl]amino}carbonyl)oxy]methyl}piperidine-1-carboxylate isomer 2 (B)

Triphosgene (117mg) was added to a solution of tert-butyl (2R,6R)-4-(hydroxymethyl)-2,6-dimethylpiperidine-1-carboxylate (192mg) and diisopropylethylamine (0.27ml) in dry THF (4ml) at room temperature under nitrogen. The mixture was stirred for 2h, then a solution of 2-(4-methyl-1,3-thiazol-2-yl)aniline (150mg) in dry THF (1ml) was added dropwise and the mixture stirred for 16h. The reaction mixture was partitioned between water (15ml) and ethyl acetate (3x15ml) and the combined organic extracts washed with brine (20ml) and dried (MgSO4). The solvent was evaporated and the residue purified by chromatography on silica. Elution with hexane / ethyl acetate 8:1 gave a mixture of the title compounds as a colourless solid (205mg)

LC/MS ESI R_T 4.55mins MH^+ 460

The racemate was separated on chiralcel OD 15ml/min, wavelength 215nm (2% ethanol / heptane) gave the title compound (A) as a colourless solid (60mg)

5048-Sample resolved on CHIRALCEL OD-H
Manufacturer DIACEL CHEMICAL INDUSTRIES LTD
Column size 0.46cm I.D. x 25cm
Column no. ODHOCE-IF029
Eluent 2% Ethanol/Heptane
Flowrate 1ml/min
Temp. RT
Wavelength 215nm
Injection volume 15ul
Retension time 30.97 mins

And the title compound (B) as a colourless solid (50mg)
Retension time 35.23 mins

Intermediate 128

tert-Butyl 4-{[({[5-fluoro-2-(4-methyl-1,3-thiazol-2-yl)phenyl]amino}carbonyl)oxy]methyl}piperidine-1-carboxylate

A solution of tert-butyl 4-(hydroxymethyl)piperidine-1-carboxylate (CAS-number 123855-51-6; 614mg) and N,N-diisopropylethylamine in dry THF (5ml) was added dropwise under nitrogen to a stirred solution of triphosgene (280mg) in dry THF (5ml) at 0°. After 2h at 0°, this mixture was added to a stirred solution of 5-fluoro-2-(4-methyl-1,3-thiazol-2-yl)aniline (594mg) and N,N-diisopropylethylamine (522µl) in THF (5ml) under nitrogen. The mixture was stirred at 0° for 3h, and then at 23° for 16h. The mixture was evaporated, treated with aqueous saturated sodium bicarbonate (30ml), and extracted with ethyl acetate (6x80ml). The combined, dried (Na_2SO_4) organic extracts were evaporated. The residue was adsorbed from warm THF (40ml) onto silica gel, and this applied to a Biotage Flash™, silica column (40g). Gradient elution with ethyl acetate-cyclohexane (4:96 to 14:86) afforded the title compound as white crystals.

LC/MS ESI R_T 4.41mins, MH^+ 450.

Intermediate 129

tert-Butyl 4-({[({[2-(4-ethyl-1,3-thiazol-2-yl)-4-fluoro]phenyl}amino)carbonyl]oxy}methyl)-piperidine-1-carboxylate

To a solution of triphosgene (75m) in dry THF (2.5ml) at 0°C, diisopropylethylenediamine (132µl) and tert-butyl-4-(hydroxymethyl)piperidine-1-carboxylate (165mg) were added and the reaction mixture was stirred at 0°C for 1.5 hours. A solution of 2-(4-ethyl-1,3-thiazol-2-yl)-4-fluoroaniline (168mg) in dry THF (2.5ml) and diisopropylethylenediamine (132µl) were added and the reaction mixture was stirred for 17 hours at room temperature. The reaction mixture was diluted with ethyl acetate (50ml) and washed with saturated aqueous sodium bicarbonate (50ml). The aqueous layer was separated and extracted with a further portion of ethyl acetate (50ml). The organics were combined, dried over $MgSO_4$ and evaporated to leave a crude yellow solid which was purified by flash column chromatography using a 4:1 hexane/ethyl acetate eluent. After evaporation the title compound was obtained as a yellow solid (321mg).

LC/MS ESI R_T 4.49mins MH^+ 464

Tlc SiO_2 (Ethyl acetate/hexane 1:1) R_f 0.51

Intermediate 130

tert-Butyl 4-({[({[2-(4-ethyl-1,3-thiazol-2-yl)-4-hydroxylphenyl}amino)carbonyl]oxy}methyl)-piperidine-1-carboxylate

To a solution of triphosgene (76mg) in dry THF (2.5ml) at 0°C, diisopropylethylenediamine (134µl) and tert-butyl-4-(hydroxymethyl)piperidine-1-carboxylate (165mg) were added and the reaction mixture was stirred at 0°C for 1.5 hours. A solution of 2-(4-ethyl-1,3-thiazol-2-yl)-4-hydroxyaniline (170mg) in dry THF (2.5ml) and diisopropylethylenediamine (134µl) were then added and reaction mixture was stirred for 17 hours at room temperature. The reaction mixture was diluted with ethyl acetate (50ml) and washed with saturated aqueous sodium bicarbonate (50ml). The aqueous layer was separated and extracted with ethyl acetate. The organics were combined, dried over $MgSO_4$, filtered and evaporated onto silica gel. The crude material was purified by flash column chromatography (dry loading) using a 4:1 hexane/ethyl acetate eluent. The title compound was obtained as a white solid (250mg).

LC/MS ESI R_T 4.33mins MH^+ 462

Tlc SiO_2 (Ethyl acetate/hexane 1:1) R_f 0.49

Example 1

Piperidin-4-ylmethyl 2-(1,3-thiazol-2-yl)phenylcarbamate trifluoroacetate

Trifluoroacetic acid (0.2ml) was added to a solution of tert-butyl 4-{[({[2-(1,3-thiazol-2-yl)phenyl]amino}carbonyl)oxy]methyl}piperidine-1-carboxylate (117mg) in dichloromethane (2ml) and the resulting solution was stirred at room temperature for 3.5h. The solvent was removed to give a yellow oil which was applied to a HPLC autoprep system and eluted with 30% to 60% acetonitrile / water. This gave the title compound as a white solid (30mg)

LC/MS ESI R_T 2.40mins MH^+ 318

NMR ($CDCl_3$ 400MHz; δ) 11.8 (1H, br s, NH) 9.37 (1H, br s, NH) 8.85 (1H, brs, NH) 8.43 (1H, brd, CH) 7.90 (1H, d, CH) 7.78 (1H, dd, CH) 7.41 (1H, ddd, CH) 7.33 (1H, d, CH) 7.09 (1H, ddd, CH) 4.10 (2H, d, CH_2) 3.48 (2H, brd, CH_2eq) 2.92 (2H, br m CH_2ax) 2.12-1.98 (3H, m +brd, CH_2 + CH_2eq) 1.67 (2H, brm, CH_2 ax)

Example 2

Piperidin-4-ylmethyl 2-(4-methyl-1,3-thiazol-2-yl)phenylcarbamate hydrochloride

A solution of tert-butyl 4-({[({2-[4-methyl-1,3-thiazol-2-yl]phenyl}amino)carbonyl]oxy}methyl) piperidine-1-carboxylate (165mg) in dry dichloromethane (8ml) and trifluoroacetic acid (0.5ml) was stirred at room temperature for 4hr under nitrogen. Basified with 8% sodium bicarbonate solution and extracted 3x dichloromethane. The combined organic extracts were dried over $MgSO_4$. The solvent was evaporated and the residue purified by chromatography (Varian Mega Bond Elut®, Si, 5g). Elution with methanol / dichloromethane / ammonia (90:10:1) gave a residue which was dissolved in methanol/dichloromethane (1:10) mixture and treated with 1N HCl in ether (0.5ml). Evaporation of the solvent gave the title compound as a white solid (80mg).

LC/MS ESI R_T 2.72mins MH^+ 332

NMR (DMSO 400MHz; δ) 11.8(1H,br.s.NH) 8.43(1H, br.d,CH) 7.73(1H,dd,CH) 7.38(1H,ddd,CH) 7.04(1H,ddd,CH) 6.87(1H,s,CH) 4.05(2H,d,CH_2) 3.13(2H,dt,2xCHeq.) 2.64(2H,ddd, 2xCHax.) 2.51(3H,s,CH_3) 1.88 (1H,m,CH) 1.78(2H,br.d, 2xCHeq.) 1.25(2H,dq, 2xCHax.)

Example 3

Piperidin-4-ylmethyl 2-(4-ethyl -1,3-thiazol-2-yl)phenylcarbamate Hydrochloride

A solution of tert-butyl 4-{[({[2-(4-ethyl-1,3-thiazol-2-yl)phenyl]amino}carbonyl)oxy]methyl} piperidine-1-carboxylate (78mg) in methanol (0.5ml) and dichloromethane (4ml) was stirred with 1N HCl in ether (1ml) at room temperature for 16hr under nitrogen. Evaporation of the solvent, trituation with ether and filtration gave the title compound as a cream solid (54mg).

LC/MS ESI R_T 2.59mins MH^+ 346

NMR (DMSO 400MHz; δ) 8.28(1H,br.d,CH) 7.87(1H,dd,CH) 7.50-7.45(2H,ddd+s, 2xCH) 7.18(1H,ddd,CH) 4.03(2H,d,CH_2) 3.28(2H,br.d, 2xCHeq.) 2.93-2.78(4H,br.t+q, 2xCHax. +CH_2) 1.98(1H,m,CH) 1.85(2H,br.d, 2XCHeq.) 1.43(2H,dq, 2xCHax.) 1.33(3H,t,CH_3)

Example 4

Piperidin-4-ylmethyl 2-(4-propyl-1,3-thiazol-2-yl)phenylcarbamate hydrochloride

A solution of tert-butyl 4-{[({[2-(4-propyl-1,3-thiazol-2-yl)phenyl]amino}carbonyl)oxy]methyl}piperidine-1-carboxylate (442mg) in ethyl acetate (10ml) and methanol (2ml) was treated with 1.0M ethereal hydrogen chloride (6.5ml) at 0°C. The mixture was then stirred for 16h at room temperature. The solvents were evaporated and the residue was triturated in ethyl acetate / ether, to give the title compound as a pale yellow powder (352mg).

NMR (DMSO 400MHz; δ) 11.9 (1H, br, s, NH), 9.05 (1H, br s, NH), 8.70 (1H, br s, NH), 8.26 (1H, br d, CH), 7.86 (1H, dd, CH), 7.50-7.45 (2H, ddd + s, 2 x CH), 7.16 (1H, ddd, CH), 4.05 (2H, d, CH_2), 3.27 (2H, br d, CH_2 EQ), 2.88 (2H, br t, CH_2 AX), 2.78 (1H, m, CH), 1.88-1.73 (4H, br d + m, 2 x CH_2), 1.45 (2H, m CH_2), 0.96 (3H, t, CH_3)

LC/MS ESI R_T 2.77 mins MH^+ 360

Tlc SiO_2 (Dichloromethane / Methanol / Ammonia 20:2:1) R_f 0.4

Example 5

Piperidin-4-ylmethyl 2-(4-isopropyl-1,3-thiazol-2-yl)phenylcarbamate hydrochloride

A solution of tert-butyl 4-{[({[2-(4-isopropyl-1,3-thiazol-2-yl)phenyl]amino}carbonyl)oxy]methyl} piperidine-1-carboxylate (57mg) in methanol(1ml) and dichloromethane (5ml) was stirred with 1N HCl in ether (1ml) at room temperature for 16hr under nitrogen. Evaporation of the solvent, trituation with ether and filtration gave the title compound as a cream solid (41mg).

LC/MS ESI R_T 2.82mins MH^+ 360

NMR (DMSO 400MHz; δ) 12.0(1H,br.s,NH) 8.90,8.55(2H, 2xv.br.s,N^+H_2) 8.28(1H,br.d,CH) 7.86(1H,dd,CH) 7.48,7.45(2H,ddd+s, 2xCH) 7.16(1H,ddd,CH) 4.04(2H,d,CH_2) 3.28(2H,br.d, 2xCHeq) 3.12(1H,m,CH) 2.88(2H,br.t, 2xCHax) 1.97(1H,m,CH) 1.34(6H,d, 2xCH_3)

Example 6

Piperidin-4-ylmethyl 2-[4-(cyclopropyl)-1,3-thiazol-2-yl]phenylcarbamate hydrochloride

A solution of tert-butyl 4-({[({2-[4-cyclopropyl-1,3-thiazol-2-yl]phenyl}amino)carbonyl]oxy}methyl) piperidine-1-carboxylate (345mg) in dry dichloromethane (11ml) and methanol (1ml) was stirred with 1N HCl in ether (2ml) at room temperature for 16hr under nitrogen. Evaporation of the solvent, trituation with ether and filtration gave the title compound as a yellow solid (254mg).

LC/MS ESI R_T 2.78mins MH^+ 358.

NMR (DMSO 400MHz; δ) 8.25(1H,br.d,CH) 7.83(1H,dd,CH) 7.50-7.43(2H,s +ddd,2xCH) 7.15 (1H,ddd,CH) 4.04 (2H,d,CH_2) 3.30(2H,br.d,2xCHeq.) 2.89 (2H,ddd,2xCHax.) 2.18(1H,m,CH) 1.98(1H,m,CH) 1.88 (2H,br.d,2xCHeq.) 1.43 (2H,br.q.2xCHax.) 1.05-0.92(4H,2xm,2xCH_2)

Example 7

Piperidin-4-ylmethyl 2-(4-butyl-1,3-thiazol-2-yl)phenylcarbamate hydrochloride

A solution of tert-butyl 4-{[({[2-(4-butyl-1,3-thiazol-2-yl) phenyl]amino}carbonyl)oxy]methyl}piperidine-1-carboxylate (660mg) in ethyl acetate (10ml) was treated with 1M ethereal hydrogen chloride (3ml) . The reaction mixture was stirred at room temperature for 16h. More ethereal hydrogen chloride (6ml) was added and the mixture was stirred for a further 16h. The mixture was then concentrated and the resultant residue was triturated in 5: 1, ether / ethyl acetate to give the title compound as a yellow powder (443mg)

NMR (DMSO 400MHz; δ) 11.9 (1H, br s, NH), 9.01 (1H, vbr s, NH), 8.67 (1H, br s, NH), 8.29 (1H, br d, CH), 7.86 (1H, dd, CH), 7.50- 7.45 (2H, ddd + s, 2 x CH), 7.16 (1H, ddd, CH), 4.03 (2H, d, CH_2), 3.27 (2H, br d, CH_2 EQ), 2.88 (2H, m, CH_2, AX),2.80 (2H, t, CH_2), 2.00 (1H, m, CH), 1.85 (2H, br d, CH_2 EQ), 1.75 (2H, m, CH_2), 1.45 (2H, m, CH_2 AX), 1.38 (2H, m, CH_2), 0.93 (3H, t, CH_3)

Tlc SiO_2 (Dichloromethane / methanol / ammonia, 20:2:1) R_f 0.44

Example 8

Piperidin-4-ylmethyl 2-(4-tert-butyl-1,3-thiazol-2-yl)phenylcarbamate hydrochloride

A solution of tert-butyl 4-{[({[2-(4-tert-butyl-1,3-thiazol-2-yl)phenyl]amino}carbonyl)oxy]methyl} piperidine-1-carboxylate (70mg) in methanol(0.5ml) and dichloromethane (5ml) was stirred with 1N HCl in ether (1ml) at room temperature for 16hr under nitrogen. Evaporation of the solvent, trituation with ether and filtration gave the title compound as a yellow solid (43mg).

LC/MS ESI R_T 2.77mins MH^+ 374

NMR (DMSO 400MHz; δ) 12.1(1H, br.s,NH) 8.30(1H,br.d,CH) 7.86(1H,dd,CH) 7.50-7.45(2H,ddd+s, 2xCH) 7.16(1H, ddd,CH) 4.03(2H,d,CH_2) 3.28(2H,br.d, 2xCHeq.) 2.88(2H,br.t, 2xCHax.) 1.95(1H,m,CH) 1.85(2H,br.d, 2xCHeq.) 1.48-1.35(11H,m +s, 2xCHax.)

Example 9

Piperidin-4-ylmethyl 2-(4-cyclobutyl-1,3-thiazol-2-yl)phenylcarbamate trifluoroacetate

Trifluoroacetic acid (0.3ml) was added to a solution of tert-butyl 4-{[({[2-(4-cyclobutyl-1,3-thiazol-2-yl)phenyl]amino}carbonyl)oxy]methyl}piperidine-1-carboxylate (285mg) in dichloromethane (3ml) and the resulting solution was stirred at room temperature for 2.5h. The solvent was removed and the residue was dried under vacuum overnight to give the title compound as a yellow solid (274mg).

LC/MS ESI R_T 2.78mins MH^+ 372

NMR ($CDCl_3$ 400MHz; δ) – 12.1 (1H, br s, NH) 8.51 (1H, brs, NH) 8.36 (1H, brd, CH) 7.74 (1H, dd, CH) 7.41 (1H, ddd, CH) 7.09 (1H, ddd, CH) 6.88 (1H, s, CH) 4.11 (2H, d, CH_2) 3.69 (1H, m, CH) 3.54 (2H, br d, CH_2 eq) 2.99 (1H, br m CH_2ax) 2.45-2.32 (1H, m, 2 x CH_2) 2.15-2.02 (4H, m, CH_2 + CH_2eq) 1.97 (1H, m, CH) 1.61 (2H, brm, CH_2 ax)

Example 10

Piperidin-4-ylmethyl 2-(4-pentyl-1,3-thiazol-2-yl)phenylcarbamate (A);

and

Piperidin-4-ylmethyl 2-(5-butyl-4-methyl-1,3-thiazol-2-yl)phenylcarbamate(B)

To a solution of tert-butyl 4-{[({[2-(4-pentyl-1,3-thiazol-2-yl)phenyl]amino}carbonyl)oxy]methyl}piperidine-1-carboxylate (1.1g) in dichloromethane (15ml) was added 1M ethereal hydrogen chloride (4ml) at 0°C.

The mixture was stirred at room temperature for 16h. More ethereal hydrogen chloride (7ml) was added and the mixture stirred for a further 16h. The solvent was evaporated and the resultant residue was purified by flash column chromatography on silica), eluting with 50:2:1 dichloromethane:methanol:ammonia solution followed by purification by mass directed HPLC to give the title compound (A) (168mg) as a white powder

LC/MS ESI R_T 3.81mins MH^+ 387

NMR ($CDCl_3$ 400MHz; δ) 12.0 (1H, br s, NH), 8.50 (1H, br s, NH), 8.42 (1H, br d, CH), 7.74 (1H, br d, CH), 7.40 (1H, br t, CH), 7.08 (1H, br t, CH), 6.88 (1H, s, CH), 7-4.5 (1H, v br s, NH), 4.10 (2H, d, CH_2), 3.42 (2H, br d, CH_2 EQ), 2.91- 2.78 (4H, m, $CH_2AX + CH_2$), 2.10- 1.94 (3H, br d + m, CH_2 EQ + CH), 1.85- 1.75 (2H, m CH_2),1.63 (2H, m, CH_2 AX), 1.40-1.30 (4H, m, 2 x CH_2), 0.91 (3H, t, CH_3)

and the title compound (B)(53mg) as a pale yellow gum.

LC/MS ESI R_T 4.18mins MH^+ 387

NMR ($CDCl_3$ 400MHz; δ) 12.0 (1H, br s, NH), 8.48 (1H, br s, NH), 9- 6 (1H, v br s, NH), 8.38 (1H, br d, CH), 7.65 (1H, br d, CH), 7.35 (1H, br t, CH), 7.03 (1H, br t, CH), 4.10 (2H, d, CH_2), 3.44 (2H, br d, CH_2 EQ), 2.88 (2H, br t, CH_2 AX), 2.75 (2H, t, CH_2), 2.38 (3H, s, CH_3), 2.1- 1.93 (3H, br d + m, CH_2 EQ + CH), 1.70- 1.58 (4H, m, CH_2 AX + CH_2), 1.40 (2H, m, CH_2), 0.95 (3H, t, CH_3)

Example 11

Piperidin-4-ylmethyl 2-(4-isobutyl-1,3-thiazol-2-yl)phenylcarbamate

To a solution of tert-butyl 4-{[({[2-(4-isobutyl-1,3-thiazol-2-yl)phenyl]amino}carbonyl)oxy]methyl}piperidine-1-carboxylate (148mg) in dry dichloromethane (3ml) was added hydrogen chloride (1M in diethyl ether; 1.5ml). Reaction was stirred for 2h at room temperature under nitrogen, then methanol (0.5ml) was added to aid solubility. Hydrogen chloride (1M in diethyl ether; 1ml) was added and mixture was stirred at room temperature for 16h, poured onto saturated aqueous sodium bicarbonate solution and extracted with ethyl acetate (x2). Combined organics were washed with brine, dried over anhydrous magnesium sulphate, filtered and evaporated in vacuo. Residue purified by Varian Mega Bond Elut® (Si, 1g); elution with 0-50% ethyl acetate in cyclohexane, dichloromethane and finally

dichloromethane: methanol: ammonia solution (9:1:0.1) gave the title compound as a white solid (79mg).

LC/MS ESI R_T 3.13mins MH^+ 374

NMR ($CDCl_3$ 400MHz; δ) 11.95 (1H,br s,NH) 8.44 (1H,br d,CH) 7.72 (1H,dd,CH) 7.38 (1H,ddd,CH) 7.05 (1H,ddd,CH) 6.85 (1H,s,CH) 4.02 (2H,d,CH_2) 3.15 (2H,br d,CH_2 eq.) 2.70-2.60 (4H,d+ddd,CH_2 +CH_2 ax.) 2.20 (1H,m,CH) 1.95-1.75 (4H+H_2O,br s+m+br d,NH+CH+CH_2 eq.) 1.28 (2H,dq,CH_2 ax.) 0.97 (6H,d,2xCH_3)

Example 12

Piperidin-4-ylmethyl 2-[4-(cyclopropylmethyl)-1,3-thiazol-2-yl]phenylcarbamate

To a solution of tert-butyl 4-({[({2-[4-(cyclopropylmethyl)-1,3-thiazol-2-yl]phenyl}amino)carbonyl]oxy}methyl)piperidine-1-carboxylate (80mg) in dry dichloromethane (5ml) was added hydrogen chloride (1M in diethyl ether; 1ml). Reaction was stirred for 30mins at room temperature under nitrogen, then dry methanol (0.5ml) was added to aid solubility and mixture was stirred for a further 2.5h. Hydrogen chloride (1M in diethyl ether; 1ml) was added and reaction stirred at room temperature for 18h. Reaction poured onto saturated aqueous sodium bicarbonate solution and extracted with ethyl acetate (x2). Combined organics were washed with brine, dried over anhydrous magnesium sulphate, filtered and evaporated in vacuo. Residue purified by Varian Mega Bond Elut® (Si, 1g); elution with 0-30% ethyl acetate in cyclohexane, dichloromethane and finally dichloromethane / methanol / ammonia solution (9:1:0.1) gave the title compound as a white residue (57mg).

LC/MS ESI R_T 2.69mins MH^+ 372

NMR ($CDCl_3$ 400MHz; δ) 11.95 (1H,br s,NH) 8.45 (1H,dd,CH) 7.73 (1H,dd,CH) 7.39 (1H,ddd,CH) 7.05 (1H,ddd,CH) 6.95 (1H,s,CH) 4.04 (2H,d,CH_2) 3.18 (2H,br d,CH_2 eq.) 2.73 (2H,d,CH_2) 2.65 (2H,ddd,CH_2 ax.) 1.88 (1H,m,CH) 1.81 (2H,br d,CH_2 eq.) 1.30 (2H,dq,CH_2 eq.) 1.15 (1H,m,CH) 0.58 (2H,m,CH_2) 0.30 (2H,m,CH_2)

Example 13

Piperidin-4-ylmethyl 2-(4-cyclopentyl-1,3-thiazol-2-yl)phenylcarbamate trifluoroacetate

Trifluoroacetic acid (0.5ml) was added to a solution of tert-butyl 4-{[({[2-(4-cyclopentyl-1,3-thiazol-2-yl)phenyl]amino}carbonyl)oxy]methyl}piperidine-1-carboxylate (26mg) in dichloromethane (5ml) and the resulting solution was stirred at room temperature for 2.5h. The solvent was removed and the residue was co-evaporated with toluene and methanol to give the title compound as a pale yellow solid (25mg).

LC/MS ESI R_T 2.86mins MH^+ 386

NMR (d^6-DMSO 400MHz; δ) 11.9 (1H, br s, NH) 8.55 (1H, br s, NH) 8.29 (1H, brd, CH) 8.23 (1H, brs, NH) 7.68 (1H, dd, CH) 7.50-7.45 (2H, ddd+s, 2XCH) 7.16 (1H, ddd, CH) 4.04 (2H, d, CH_2) 3.35-3.22 (3H, m, CH_2 + CH –signals obscured by water) 2.90 (2H, br m, CH_2 ax) 2.11 (1H, m, CH_2) 1.95 (1H, m, CH) 1.85 (2H, br d, CH_{2eq}) 1.81-1.63 (6H, m, CH_2rest) 1.39δ (2H, brm, CH_2ax)

Example 14

Piperidin-4-ylmethyl 2-(4-cyclohexyl-1,3-thiazol-2-yl)phenylcarbamate trifluoroacetate

Trifluoroacetic acid (0.5ml) was added to a solution of tert-butyl 4-{[({[2-(4-cyclohexyl-1,3-thiazol-2-yl)phenyl]amino}carbonyl)oxy]methyl}piperidine-1-carboxylate (63mg) in dichloromethane (5ml) and the resulting solution was stirred at room temperature for 2.5h. The solvent was removed and the residue was co-evaporated with toluene and methanol to give the title compound as a pale yellow solid (63mg).

LC/MS ESI R_T 2.94mins MH^+ 400

NMR (d^6 DMSO 400MHz; δ) 12.0 (1H, br s, NH) 8.55 (1H, br m, NH) 8.30 (1H, brd, CH) 8.25 (1H, brs, NH) 7.85 (1H, dd, CH) 7.48 (1H, ddd, CH) 7.42 (1H, s, CH) 7.15 (1H, ddd, CH) 4.04 (2H, d, CH_2) 3.30 (2H, brd, CH_2eq) 2.90 (2H, br m, CH_2 ax) 2.79 (1H, tt,CHax) 2.08 (1H, brd, CH_2eq) 1.97 (1H, m, CH) 1.90-1.70 (5H, m, CH_2eq +0.5 CH_2eq) 1.58-1.35 (6H, m, 3 x CH_2ax) 1.22 (1H, qt, 0.5CH_2ax)

Example 15

Piperidin-4-ylmethyl 2-(4-phenyl-1,3-thiazol-2-yl)phenylcarbamate hydrochloride

A solution of tert-butyl 4-{[({[2-(4-phenyl-1,3-thiazol-2-yl)phenyl]amino}carbonyl)oxy]methyl} piperidine-1-carboxylate (74mg) in

methanol(0.5ml) and dichloromethane (5ml) was stirred with 1N HCl in ether (1ml) at room temperature for 16hr under nitrogen. Evaporation of the solvent, trituation with ether and filtration gave the title compound as a cream solid (54mg).

LC/MS ESI R_T 2.78mins MH^+ 394

NMR (DMSO 400MHz; δ) 8.45-8.40(2H,brd+s,2xCH) 8.15(2H,dd,2xCH) 8.06(1H,dd,CH) 7.67-7.59(3H,m,3xCH) 7.55(1H,ddd,CH) 7.31(1H,ddd,CH) 4.20(2H,d,CH_2) 3.40(2H,br.d,2xCHeq. +H_2O) 3.02(2H,ddd,2xCHax.) 2.15(1H,m,CH) 2.00(2H, br.d,2xCHeq.) 1.58(2H,dq,2xCHax.)

Example 16

Piperidin-4-ylmethyl 2-(4-thien-3-yl-1,3-thiazol-2-yl)phenylcarbamate hydrochloride

A solution of tert-butyl 4-{[({[2-(4-thien-3-yl-1,3-thiazol-2-yl)phenyl]amino}carbonyl)oxy]methyl} piperidine-1-carboxylate (101mg) in methanol(0.5ml) and dichloromethane (5ml) was stirred with 1N HCl in ether (1ml) at room temperature for 16hr under nitrogen. Evaporation of the solvent, trituation with ether and filtration gave the title compound as a cream solid (69mg).

LC/MS ESI R_T 2.74mins MH^+ 400

NMR (DMSO 400MHz; δ) 8.07(1H,br.d,CH) 7.90(1H,s,CH) 7.74(1H,dd,CH) 7.69(1H,dd,CH) 7.50(1H,dd,CH) 7.48(1H,dd,CH) 7.28(1H,ddd,CH) 6.97(1H,ddd,CH) 3.48(2H,d,CH_2) 3.04(2H,br.d, 2xCHeq.) 2.68(2H,br,t, 2xCHax.) 1.80(1H,m,CH) 1.65(2H,br.d, 2xCHwq.) 1.22(2H,dq, 2xCHax.)

Example 17

4-[({[(2-{4-[(Dimethylamino)methyl]-1,3-thiazol-2-yl}phenyl)amino]carbonyl}oxy)methyl]piperidine trifluoroacetate

tert-Butyl 4-[({[(2-{4-[(dimethylamino)methyl]-1,3-thiazol-2-yl}phenyl)amino]carbonyl}oxy)methyl]piperidine-1-carboxylate (30mg) was dissolved in trifluoroacetic acid (1ml) and water (0.1ml) added. The solution was stirred at 20°C for 2.5 hours before evaporating and drying overnight *in vacuo* to yield the title compound (28.9mg).

NMR ($CDCl_3$, 400MHz, δ) 12.55 (1H,br s,NH^+) 11.3 (1H,s,NH) 9.50 (1H,br d,NH^+) 8.90 (1H,br d,NH^+) 8.45 (1H,br d,aromatic CH) 7.76 (1H,dd,aromatic CH) 7.69

(1H,s,aromatic.CH) 7.47 (1H,dt,aromatic CH) 7.12 (1H,dt,aromatic CH) 4.48 (2H,s,CH_2) 4.16 (2H,d,CH_2) 3.51 (2H,br d,CH_2) 2.98 (2H,br d,CH_2) 2.91 (6H,s,2CH_3) 1.99 (1H,m,CH) 1.94 – 1.75 (4H,m,2CH_2).

Example 18

Piperidin-4-ylmethyl 2-[4-(hydroxymethyl)-1,3-thiazol-2-yl]phenylcarbamate hydrochloride

tert-Butyl 4-({[({2-[4-(hydroxymethyl)-1,3-thiazol-2-yl]phenyl}amino)carbonyl]oxy}methyl)piperidine-1-carboxylate (84mg) was suspended in hydrochloric acid (1M in diethyl ether (5ml) and stirred for 4 hours before evaporating to dryness to yield the title compound (61mg).

NMR (D_2O, 400MHz, δ) 7.77 (1H,dd,aromatic CH) 7.64 (1H,br d,aromatic CH) 7.47 (1H,s,aromatic CH) 7.46 (1H,dt,aromatic CH) 7.29 (1H,br t,aromatic CH) 4.68 (2H,s,CH_2) 3.94 (2H,d,CH_2) 3.38 (2H,br d,CH_2) 2.93 (2H,br t,CH_2) 1.90 (1H,m,CH) 1.86 (2H,br d,CH_2) 1.40 (2H,br q,CH_2)

Example 19

Piperidin-4-ylmethyl 2-[4-(methoxymethyl)-1,3-thiazol-2-yl]phenylcarbamate trifluoroacetate

Tert-butyl 4-({[({2-[4-(methoxymethyl)-1,3-thiazol-2-yl]phenyl}amino)carbonyl]oxy}methyl)piperidine-1-carboxylate (8.5mg) was dissolved in trifluoroacetic acid (1ml) and water (0.1ml) added. The solution formed a suspension after 5 minutes, and was stirred for a further 90 minutes at 20°C before evaporating to dryness to yield the title compound (10.6mg).

NMR ($CDCl_3$, 400MHz, δ) 11.8 (1H,br s,NH) 9.05 (1H,br s, NH^+) 8.39 (1H,d,aromatic CH) 8.32 (1H,br s, NH^+) 7.74 (1H,dd,aromatic CH), 7.41 (dt,aromatic CH) 7.23 (1H,s,aromatic CH)) 7.09 (1H,dt,aromatic CH) 4.64 (2H,s,CH_2) 4.12 (2H,d,CH_2) 3.52 (2H,br d,CH_2) 3.48 (3H,s,CH_3) 2.99 (2H,br q,CH_2) 2.05 (3H,br d,CH_3) 1.69 (2H,br q,CH_2) .

Example 20

Piperidin-4-ylmethyl 2-{4-[(methylamino)carbonyl]-1,3-thiazol-2-yl}phenylcarbamate trifluoroacetate

Tert-butyl 4-[({[(2-{4-[(methylamino)carbonyl]-1,3-thiazol-2-yl}phenyl)amino]carbonyl}oxy)methyl]piperidine-1-carboxylate (17.8mg) was dissolved in trifluoroacetic acid (1ml) and water (0.1ml) added. The solution was stirred for 1hr at 20°C before evaporating and drying *in vacuo* to yield the title compound (17.8mg).

NMR ($CDCl_3$, 400MHz, δ) 11.1 (1H,br s,NH) 9.11 (1H,br s,NH^+) 8.65 (1H,br s,NH^+) 8.35 (1H,d,aromatic CH) 8.13 (1H,s,aromatic CH) 7.73 (1H,dd,aromatic CH) 7.48 (dt,aromatic CH) 7.18 (1H,br q,NH) 7.13 (1H,dt,aromatic CH) 4.17 (2H,d, CH_2) 3.52 (2H,br d,CH_2) 3.03 (3H,d,CH_3) 2.96 (2H,br q,CH_2) 2.06 (1H,m,CH) 2.00 (2H,br d,CH_2) 1.73 (2H,br q,CH_2)

Example 21

Ethyl 2-(2-{[(piperidin-4-ylmethoxy)carbonyl]amino}phenyl)-1,3-thiazole-4-carboxylate trifluoroacetate

Tert-butyl 4-({[({2-[4-(ethoxycarbonyl)-1,3-thiazol-2-yl]phenyl}amino)carbonyl]oxy}methyl)piperidine-1-carboxylate (50mg) was dissolved in trifluoroacetic acid (1ml) and water (0.1ml) added. The solution was stirred for 1hr at 20°C before evaporating and drying in vacuo to yield the title compound (56.8mg).

NMR ($CDCl_3$, 400MHz, δ) 11.9 (1H,br s,NH) 9.25 (1H,br s,NH^+) 8.42 (1H,d,aromatic CH) 8.14 (1H,s,aromatic CH) 7.76 (1H,dd,aromatic CH) 7.49 (1H,br s,NH^+) 7.48 (dt,aromatic CH) 7.11 (1H,dt,aromatic CH) 4.39 (2H,q,CH_2) 4.19 (2H,d,CH_2) 3.62 (2H,br d,CH_2) 3.12 (2H,br q,CH_2) 2.02 (4H,m,$2CH_2$) 1.40 (3H,t,CH_3)

Example 22

Piperidin-4-ylmethyl 2-{4-[2-(benzyloxy)ethyl]-1,3-thiazol-2-yl}phenylcarbamate trifluoroacetate

To a solution of tert-butyl 4-[({[(2-{4-[2-(benzyloxy)ethyl]-1,3-thiazol-2-yl}phenyl)amino]carbonyl}oxy)methyl]piperidine-1-carboxylate (100mg) in dichloromethane (1ml) was added trifluoroacetic acid (0.13ml). After stirring for 24 hours at room temperature, the solvents were evaporated. The crude residue was

triturated with diethyl ether, evaporated and dried under vacuum to give the title compound as brown solid (114mg).

NMR (d^6-DMSO 400MHz; δ) 11.87 (1H,s,NH) 8.53 (1H,br. s, NH_2^+)8.26 (1H,d,aromatic CH) 8.21 (1H,br. s, NH_2^+) 7.86 (1H,d,aromatic CH) 7.53 (1H,s,thiazole CH) 7.47 (1H,t,aromatic CH) 7.32-7.21 (5H,m,phenyl) 7.17 (1H,t,aromatic CH) 4.51 (2H,s,OCH_2Ar) 4.00 (2H,d,OCH_2piperidine) 3.87 (2H,t,O CH_2) 3.27 (2H,br. d, CH_2N^+) 3.09 (2H,t,thiazole CH_2) 2.92-2.80 (2H,m, CH_2N^+) 1.98-1.87 (1H,m, CH_2 of piperidine ring) 1.82 (2H,br. d, CH_2 of piperidine ring) 1.43-1.31 (2H,m, CH_2 of piperidine ring).

LC/MS ESI R_T 3.13mins, MH^+ 452.6

Example 23

Piperidin-4-ylmethyl 2-(4-acetyl-1,3-thiazol-2-yl)phenylcarbamate trifluoroacetate

To a solution tert-butyl 4-{[({[2-(4-acetyl-1,3-thiazol-2-yl)phenyl]amino}carbonyl)oxy]methyl}piperidine-1-carboxylate (19mg) in dichloromethane (0.5ml) was added trifluoroacetic acid (0.05ml). After stirring for 90 mins at room temperature, the solvents were evaporated. The crude oil was triturated with diethyl ether to give, after drying, the title compound as a white solid (21mg).

NMR (d^6-DMSO 400MHz; δ) 11.75 (1H,s,NH) 8.65 (1H,s,thiazole CH) 8.53 (1H,br. s,NH^+) 8.25 (1H,d,aromatic CH) 7.98 (1H,d, aromatic CH) 7.55 (1H,t,aromatic CH) 4.05 (2H,d,OCH_2) 3.30 (2H,m, CH_2N^+) 2.96-2.83 (2H,m, CH_2N^+) 2.67 (3H,s, CH_3) 2.02-1.91 (1H,m, CH of piperidine ring) 1.90-1.81 (2H,m, CH_2 of piperidine ring) 1.45-1.32 (2H,m, CH_2 of piperidine ring).

LC/MS ESI R_T 2.56mins, MH^+ 360.5

Example 24

Piperidin-4-ylmethyl 2-[4-(1-hydroxyethyl)-1,3-thiazol-2-yl]phenylcarbamate

To a solution tert-butyl 4-({[({2-[4-(1-hydroxyethyl)-1,3-thiazol-2-yl]phenyl}amino)carbonyl]oxy}methyl)piperidine-1-carboxylate (41mg) in dichloromethane (1ml) was added trifluoroacetic acid (0.07ml). After stirring for 18 hours at room temperature, the solvents were evaporated. The crude oil was re-dissolved in ethyl acetate, washed with saturated aqueous sodium bicarbonate

and water then dried ($MgSO_4$). The solvent was evaporated to give, after drying the title compound as a pale yellow solid (33mg).

NMR (d^6-DMSO 400MHz; δ) 11.88 (1H,s,NH) 8.24 (1H,d,aromatic CH) 7.87 (1H,d,aromatic CH) 7.54 (1H,s,thiazole CH) 7.46 (1H,t,aromatic CH) 7.17 (1H,t,aromatic CH) 4.88 (1H,q,CHOH) 4.03-3.98 (2H,m,OCH_2) 3.12-3.03 (2H,m, CH_2N) 2.70-2.57 (2H,m, CH_2N) 1.88-1.77 (1H,m,CH of piperidine ring) 1.76-1.67 (2H,m, CH_2 of piperidine ring) 1.48 (3H,d,CH_3) 1.32-1.03 (2H,m, CH_2 of piperidine ring).

LC/MS ESI R_T 2.54mins, MH^+ 362.2

Example 25

(*R*)-Piperidin-4-ylmethyl 2-[4-(1-hydroxyethyl)-1,3-thiazol-2-yl]phenylcarbamate hydrochloride

To a solution (*R*)-tert-butyl 4-({[({2-[4-(1-hydroxyethyl)-1,3-thiazol-2-yl]phenyl}amino)carbonyl]oxy}methyl)piperidine-1-carboxylate (150mg) methanol (3ml) was added a 1M solution of hydrogen chloride in diethyl ether (15ml). After stirring for 3 hours at room temperature, the solvents were evaporated to give after drying the title compound as a pale yellow solid (141mg).

NMR (d^6-DMSO 400MHz; δ) 11.79 (1H,s,NH) 8.71 (1H,br. s,NH_2^+) 8.36 (1H,br. s,NH_2^+) 8.25 (1H,d,aromatic CH) 7.87 (1H,d,aromatic CH) 7.54 (1H,s,thiazole CH) 7.47 (1H,t,aromatic CH) 7.17 (1H,t,aromatic CH) 5.51 (1H,br. s,OH) 4.89 (1H,q,CHOH) 4.03 (2H,d,OCH_2) 3.32-3.25 (2H,m, CH_2N) 2.94-2.82 (2H,m, CH_2N) 2.00-1.91 (1H,m,CH of piperidine ring) 1.88-1.82 (2H,m, CH_2 of piperidine ring) 1.50 (3H,d,CH_3) 1.32-1.03 (2H,m, CH_2 of piperidine ring).

LC/MS ESI R_T 2.55mins, MH^+ 362

Example 26

Piperidin-4-ylmethyl 2-[4-(2-hydroxyethyl)-1,3-thiazol-2-yl]phenylcarbamate hydrochloride

To solution of tert-Butyl 4-({[({2-[4-(2-hydroxyethyl)-1,3-thiazol-2-yl]phenyl}amino)carbonyl]oxy}methyl)piperidine-1-carboxylate (100mg) in methanol (1ml) was added a 1M hydrogen chloride solution in diethyl ether (5ml). After stirring

for 3 hours at room temperature, the solvents were evaporated. The crude oil was triturated with diethyl ether and after drying under vacuum the title compound was obtained as a pale yellow solid (96.2mg).

NMR (d^6-DMSO 400MHz; δ) 11.82 (1H,s,NH) 8.85 (1H,br s,NH_2^+) 8.48 (1H,br s,NH_2^+) 8.25 (1H,d,aromatic CH) 7.86 (1H,d,aromatic CH) 7.48 (1H,s,thiazole CH) 7.45 (1H,t,aromatic CH) 7.17 (1H,t,aromatic CH) 4.04 (2H,d, OCH_2) 3.83 (2H,t,CH_2OH) 3.32-3.23 (2H,m,CH_2N) 2.94 (2H,t,CH_2) 2.93-2.82 (2H,m,CH_2N) 2.04-1.92 (1H,m,CH of piperidine ring) 1.90-1.82 (2H,m, CH_2 of piperidine ring) 1.50-1.46 (2H,m,CH_2 of piperidine ring).

LC/MS ESI R_T 2.60mins, MH^+ 362.3

Example 27

Piperidin-4-ylmethyl 2-[4-(trifluoromethyl)-1,3-thiazol-2-yl]phenylcarbamate hydrochloride.

A solution of tert-butyl 4-({[({2-[4-trifluoromethyl-1,3-thiazol-2-yl]phenyl}amino)carbonyl]oxy} methyl) piperidine-1-carboxylate (60mg) in dry dichloromethane (3ml) and methanol (0.5ml) was stirred with 1N HCl in ether (1ml) at room temperature for 16hr under nitrogen. Evaporation of the solvent, trituation with ether and filtration gave the title compound as a yellow solid (38mg).

LC/MS ESI R_T 2.58mins MH^+ 386

NMR (DMSO 400MHz; δ) 8.65 (1H,s,CH) 8.04-7.95 (2H,m,2xCH) 7.57 (1H,ddd,CH) 7.30(1H,ddd,CH) 4.00(2H,d,CH_2) 3.28(2H,br.d,2xCHeq.) 2.88 (2H,m,2xCHax.) 1.95(1H,m,CH) 1.81(2H,br.d,2xCHeq.) 1.38(2H,br.q.2xCHax.)

Example 28

Piperidin-4-ylmethyl 2-[4-(difluoromethyl)-1,3-thiazol-2-yl]phenylcarbamate

To a solution tert-butyl 4-({[({2-[4-(difluoromethyl)-1,3-thiazol-2-yl]phenyl}amino)carbonyl]oxy}methyl)piperidine-1-carboxylate (85mg) in dichloromethane (1ml) was added trifluoroacetic acid (0.27ml). After stirring for 2 hours 45 mins at room temperature, the solvents were evaporated. The crude oil was re-dissolved in ethyl acetate and washed with 0.5 M aqueous sodium hydroxide then

water. The solvent was evaporated to give, after drying the title compound as a pale yellow solid (63mg).

NMR ($CDCl_3$ 400MHz; δ) 11.78 (1H,s,NH) 8.40 (1H,d,aromatic CH) 7.75 (1H,d,aromatic CH) 7.43 (1H,t,aromatic CH) 7.36 (1H,s,thiazole CH) 7.09 (1H,t,aromatic CH) 5.50 (2H,d, CH_2F), 4.11 (2H,d,OCH_2) 3.45 (2H,br. d, CH_2N) 2.92 (2H,br. t, CH_2N), 2.08-1.96 (3H,m,CH and CH_2 of piperidine ring) 1.74-1.61 (2H,m, CH_2 of piperidine ring)

LC/MS ESI R_T 2.45mins, MH^+ 367.4

Example 29

Piperidin-4-ylmethyl 2-[4-(fluoromethyl)-1,3-thiazol-2-yl]phenylcarbamate trifluoroacetate

To a solution tert-butyl 4-({[({2-[4-(fluoromethyl)-1,3-thiazol-2-yl]phenyl}amino)carbonyl]oxy}methyl)piperidine-1-carboxylate (45mg) in dichloromethane (2ml) was added trifluoroacetic acid (0.13ml). After stirring for 3 hours at room temperature, the solvents were evaporated. The crude oil was triturated with diethyl ether to give, after drying, the title compound as a white solid (46mg).

NMR (d^6-DMSO 400MHz; δ) 11.44 (1H,s,NH) 8.53 (1H,br. s,NH_2^+) 8.22 (1H,s,thiazole CH) 8.20 (1H,br. s, NH_2^+) 8.08 (1H,d,aromatic CH) 7.94 (1H,d,aromatic CH) 7.50 (1H,t,aromatic CH) 7.23 (1H,t,aromatic CH) 7.16 (1H,t,CF_2H) 4.00 (2H,d,OCH_2) 3.34-3.22 (2H,m, CH_2N^+) 2.93-2.80 (2H,m, CH_2N^+) 2.00-1.87 (1H,m,CH of piperidine ring) 1.86-1.77 (2H,m, CH_2 of piperidine ring) 1.42-1.28 (2H,m, CH_2 of piperidine ring).

LC/MS ESI R_T 2.43mins, MH^+ 350.4

Example 30

Piperidin-4-ylmethyl 2-[4-(1,1-difluoroethyl)-1,3-thiazol-2-yl]phenylcarbamate

To a solution of tert-butyl 4-({[({2-[4-(1,1-difluoroethyl)-1,3-thiazol-2-yl]phenyl}amino)carbonyl]oxy}methyl)piperidine-1-carboxylate (40mg) in dichloromethane (3ml) was added trifluoroacetic acid (0.21ml). After stirring for 5 hours at room temperature, the solvents were evaporated. The crude residue was re-dissolved in ethyl acetate and washed with 0.5M sodium hydroxide then water. After

drying ($MgSO_4$), the solvent was evaporated to give a pale brown residue which was further purify by mass directed preparative HPLC to afford the title compound as white solid (5mg).

NMR ($CDCl_3$ 400MHz; δ) 11.76 (1H,s,NHCO) 8.54 (1H,s,piperidine NH) 8.42 (1H,d,aromatic CH) 7.74 (1H,d,aromatic CH) 7.54 (1H,s,thiazole CH) 7.43 (1H,t,aromatic CH) 7.08 (1H,t,aromatic CH) 4.09 (1H,d,OCH_2) 3.45-3.33 (2H,m, CH_2N) 2.88-2.75 (2H,m, CH_2N) 2.08 (3H,t, CH_3CF_2) 2.00-1.90 (3H,m,CH and CH_2 of piperidine ring) 1.69-1.53 (2H,m, CH_2 of piperidine ring)

LC/MS ESI R_T 2.73mins, MH^+ 382.5

Example 31

Piperidin-4-ylmethyl 2-[4-(2-fluoroethyl)-1,3-thiazol-2-yl]phenylcarbamate

To a solution of tert-butyl 4-({[({2-[4-(2-fluoroethyl)-1,3-thiazol-2-yl]phenyl}amino)carbonyl]oxy}methyl)piperidine-1-carboxylate (55mg) in dichloromethane (1ml) was added trifluoroacetic acid (0.05ml). After stirring for 3 hours at room temperature, the solvents were evaporated. The crude oil was re-dissolved in ethyl acetate and washed with 0.5 M aqueous sodium hydroxide then water. The solvent was evaporated to give, after drying, the title compound as a pale brown solid (35mg).

NMR ($CDCl_3$ 400MHz; δ) 11.89 (1H,s,NH) 8.42 (1H,d,aromatic CH) 7.73 (1H,d,aromatic CH) 7.40 (1H,t,aromatic CH) 7.05 (1H,t,aromatic CH) 7.02 (1H,s, thiazole CH) 4.88 (1H,dt, CH_2F) 4.05 (2H,d,OCH_2) 3.24 (2H,dt,thiazol- CH_2) 3.21-3.13 (2H,m, CH_2NH) 2.68 (2H,td, CH_2NH) 1.90-1.60 (3H,m,CH_2 and CH of piperidine ring) 1.37-1.25 (2H,m, CH_2 of piperidine ring)

LC/MS ESI R_T 2.77mins, MH^+ 364.2

Example 32

Piperidin-4-ylmethyl 2-[4-(2,2-difluoroethyl)-1,3-thiazol-2-yl]phenylcarbamate trifluoroacetate

A solution of *tert*-butyl 4-({[({2-[4-(2,2-difluoroethyl)-1,3-thiazol-2-yl]phenyl}amino)carbonyl]oxy}methyl)piperidine-1-carboxylate (46mg) and trifluoroacetic acid (0.1ml) in dichloromethane (3ml) was stirred at room temperature

for 2 hours 20 minutes. After evaporation of the residue, the residue was triturated with diethyl ether. After drying under vacuum for 12 hours, the title compound was obtained as a pale yellow solid (49mg).

NMR ($CDCl_3$ 400MHz; δ) 11.45 (1H,s,NH) 8.22 (1H,br d,aromatic CH) 7.90 (1H,dd,aromatic CH) 7.70 (1H,s,thiazole CH) 7.49 (1H,dt,aromatic CH) 7.19 (1H,dt,aromatic CH) 6.41 (1H,tt,CF_2H) 4.03 (2H,d,OCH_2) 3.46 (2H,dt,CH_2CF_2) 3.32-3.25 (2H,m,CH_2N) 2.89 (2H,bt,CH_2N) 2.01-1.90 (1H,m,piperidine CH) 1.86 (2H, br d,piperidine CH_2) 1.45-1.31 (2H,m,piperidine CH_2).

LC/MS ESI R_T 2.88mins MH^+ 382.4

Example 33

Piperidin-4-ylmethyl 2-(4,5-dimethyl -1,3-thiazol-2-yl)phenylcarbamate hydrochloride

A solution of tert-butyl 4-{[({[2-(4,5-dimethyl-1,3-thiazol-2-yl)phenyl]amino}carbonyl)oxy]methyl} piperidine-1-carboxylate (55mg) in methanol(0.5ml) and dichloromethane (5ml) was stirred with 1N HCl in ether (1ml) at room temperature for 16hr under nitrogen. Evaporation of the solvent, trituation with ether and filtration gave the title compound as a yellow solid (42mg).

LC/MS ESI R_T 2.60mins MH^+ 346

NMR (DMSO 400MHz; δ) 8.04(1H,br.d,CH) 7.56(1H,dd,CH) 7.23(1H,ddd,CH) 6.95(1H,ddd,CH) 3.85(2H,d,CH_2) 3.09(2H,br.d, 2xCHeq.) 2.69(2H, m, 2xCHax.) 2.22(3H,s,CH_3) 2.18(3H,s,CH_3) 1.78(1H,m,CH) 1.65(2H,br.d, 2xCHeq.) 1.25(2H,br.q, 2xCHax.)

Example 34

Piperidin-4-ylmethyl 2-(5-methyl-1,3-thiazol-2-yl)phenylcarbamate hydrochloride

A solution of tert-butyl 4-{[({[2-(5-methyl-1,3-thiazol-2-yl)phenyl]amino}carbonyl)oxy]methyl} piperidine-1-carboxylate (97mg) in methanol(1ml) and dichloromethane (5ml) was stirred with 1N HCl in ether (1ml) at room temperature for 16hr under nitrogen. Evaporation of the solvent, trituation with ether and filtration gave the title compound as a cream solid (77mg).

LC/MS ESI R_T 2.49mins MH^+ 332

NMR (DMSO 400MHz; δ) 8.26(1H,br.d,CH) 7.80(1H,dd,CH) 7.73(1H,s,CH) 7.46(1H,ddd,CH) 7.18(1H,ddd,CH) 4.05(2H,d,CH_2) 3.28(2H,br.d, 2xCHeq.) 2.87(2H,br.m, 2xCHax.) 2.52(3H,s,CH3 obscured by DMSO) 2.00(1H,m,CH) 1.83(2H,br.d, 2xCHeq.) 1.42(2H,br.q, 2xCHax)

Example 35

Piperidin-4-ylmethyl 2-{4-methyl-5-[(methylamino)carbonyl]-1,3-thiazol-2-yl}phenylcarbamate trifluoroacetate

To a solution of tert-butyl 4-[({[(2-{4-methyl-5-[(methylamino)carbonyl]-1,3-thiazol-2-yl}phenyl)amino]carbonyl}oxy)methyl]piperidine-1-carboxylate (50mg) in dichloromethane(5ml) was added trifluoracetic acid (2ml). The mixture was stirred at room temperature for 2h. The solvents were then evaporated to leave the title compound as a pale yellow foam (40mg).

NMR ($CDCl_3$ 400MHz; δ) 11.7 (1H, s, NH) 9.03 (1H, br s, NH) 8.52 (1H, br s, NH), 8.39 (1H, br d, CH), 7.67 (1H, dd, CH), 7.42 (1H, ddd, CH), 7.065 (1H, ddd, CH), [6.95 – excess CF_3COOH], 6.07 (1H, br q, NH), 4.11 (2H, d, CH_2), 3.52 (2H, br d, CH_2 EQ), 3.01 (3H, s, CH_3), 3.0- 2.90 (2H, br t, CH_2 AX), 2.70 (3H, s, CH_3), 2.10- 1.93 (3H, br m, CH + CH_2 EQ), 1.68 (2H, br m, CH_2 AX)

LC/MS ESI R_T 2.49mins MH^+ 389

Tlc SiO_2 (Dichloromethane / methanol / ammonia, 20:2:1) R_f 0.1

Example 36

Piperidin-4-ylmethyl 2-(4,5,6,7-tetrahydro[1,3]thiazolo[5,4-c]pyridin-2-yl)phenylcarbamate

To a solution of tert-butyl 2-{2-[({[1-(tert-butoxycarbonyl)piperidin-4-yl]methoxy}carbonyl)amino]phenyl}-6,7-dihydro[1,3]thiazolo[5,4-c]pyridine-5(4H)-carboxylate (27mg) in dry dichloromethane (2ml) was added hydrogen chloride (1M in diethyl ether; 1ml). Reaction was stirred for 1h at room temperature under nitrogen, then dry methanol (0.5ml) was added to aid solubility. Hydrogen chloride (1M in diethyl ether; 1ml) was added and mixture was stirred at room temperature for 18h. Reaction evaporated in vacuo and residue purified by Varian Mega Bond Elut® (Si, 0.5g); elution with 0-100% ethyl acetate in cyclohexane, dichloromethane and finally

dichloromethane: methanol: ammonia solution (98:2:0.2 to 85:15:1.5) gave the title compound as an off white residue (15mg).

LC/MS ESI R_T 2.16mins MH^+ 373

NMR (DMSO 400MHz; δ) 11.6 (1H,br s,NH) 8.22 (1H,br d,CH) 7.80 (1H,dd,CH) 7.45 (1H,ddd,CH) 7.15 (1H,ddd,CH) 4.10 (1H,br s,NH) 4.00 (2H,d,CH_2) 3.95 (2H,s,CH_2) 3.11 (2H,br dt,CH_2 eq.) 3.03 (2H,t,CH_2) 2.75 (2H,br t,CH_2) 2.68 (2H,ddd,CH_2 ax.) 1.85 (1H,m,CH) 1.72 (2H,br d,CH_2 eq.) 1.26 (2H,dq,CH_2)

Example 37

Piperidin-4-ylmethyl 2-(5,6-dihydro-4H-cyclopenta[d][1,3]thiazol-2-yl)phenylcarbamate

To a solution of tert-butyl 4-{[({[2-(5,6-dihydro-4H-cyclopenta[d][1,3]thiazol-2-yl)phenyl]amino}carbonyl)oxy]methyl}piperidine-1-carboxylate (162mg) in dry dichloromethane (3ml) was added hydrogen chloride (4M in 1,4-dioxane; 1ml). Reaction was stirred for 15mins at room temperature under nitrogen, then dry methanol (0.5ml) was added to aid solubility. The mixture was stirred at room temperature for 18h, evaporated in vacuo and the residue purified by Varian Mega Bond Elut® (Si, 5g). Elution with dichloromethane followed by dichloromethane: methanol: ammonia solution (99:1:0.1 to 90:10:1) gave the title compound as a white solid (105mg).

LC/MS ESI R_T 3.00mins MH^+ 358

NMR (DMSO 400MHz; δ) 11.4 (1H,br s,NH) 8.23 (1H,br d,CH) 7.82 (1H,br d,CH) 7.45 (1H,ddd,CH) 7.16 (1H,ddd,CH) 4.02 (2H,d,CH_2) 3.18 (2H,br d,CH_2 eq.) 2.96 (2H,br t,CH_2) 2.88 (2H,br t,CH_2) 2.75 (2H,ddd,CH_2 ax.) 2.50 (2H,m,CH_2 obscured by DMSO) 1.92 (1H,m,CH) 1.77 (2H,br d,CH_2 eq.) 1.33 (2H,dq,CH_2 ax.)

Example 38

Piperidin-4-ylmethyl 2-[4-bromo-1,3-thiazol-2-yl]phenylcarbamate trifluoroacetate

A solution of *tert*-butyl 4-({[({2-[4-bromo-1,3-thiazol-2-yl]phenyl}amino)carbonyl]oxy}methyl)piperidine-1-carboxylate (101 mg) and trifluoroacetic acid (0.3 ml) in dichloromethane (5 ml) was stirred at room temperature for 6 hours. After evaporation of the solvent, the residue was dryied under vacuum for 12 hours to give the title compound as a pale yellow solid solid (102 mg).

LC/MS ESI R_T 2.66 mins $M+2H^+$ 398

Example 39

Piperidin-4-ylmethyl 2-[4-chloro-1,3-thiazol-2-yl]phenylcarbamate trifluoroacetate

A solution of *tert*-butyl 4-({[({2-[4-chloro-1,3-thiazol-2-yl]phenyl}amino)carbonyl]oxy}methyl)piperidine-1-carboxylate (150 mg) and trifluoroacetic acid (0.5 ml) in dichloromethane (7.5 ml) was stirred at room temperature for 16 hours. After evaporation of the solvent, the residue was dried under vacuum for 12 hours to give the title compound as a pale yellow solid (156 mg).

LC/MS ESI R_T 2.72 mins MH^+ 352

Example 41

Piperidin-4-ylmethyl 5-fluoro-2-(4-methyl-1,3-thiazol-2-yl)phenylcarbamate hydrochloride

A solution of tert-butyl 4-{[({[5-fluoro-2-(4-methyl-1,3-thiazol-2-yl)phenyl]amino}carbonyl)oxy]methyl}piperidine-1-carboxylate (300mg) in dichloromethane was treated with a solution of 4.0M hydrogen chloride in 1,4-dioxan (2ml) at 23° and stirred for 1.5h. The mixture was evaporated to give the title compound as cream crystals (228mg).

NMR (D_2O 400MHz; δ) 7.48-7.39 (2H, m, 2xaromatic CH), 6.88 (1H,s,oxazole CH), 6.66 (1H, m, aromatic CH), 3.77 (2H, d, CH_2), 3.21 (2H, m, CH_2), 2.77 (2H, m, CH_2), 2.14 (3H, s, CH_3), 1.83-1.68 (3H, m, CH&CH_2), 1.25 (2H, m, CH_2).

LC/MS ESI R_T 2.96mins, MH^+ 350.

Example 42

Piperidine-4-ylmethyl(2-{4-ethyl-1,3-thiazol-2-yl}4-fluoro)phenylcarbamate trifluoro acetate

To a solution of tert-butyl 4-({[({[2-(4-ethyl-1,3-thiazol-2-yl)-4-fluoro]phenyl}amino)carbonyl]oxy} methyl)-piperidine-1-carboxylate (100mg) in DCM (5ml) 10% TFA (331µl) was added. The reaction mixture was stirred for 5 hours at room temperature then evaporated to give the title compound as a yellow solid (110mg).

LC/MS ESI R_T 3.04mins MH^+ 364

NMR (d^6 DMSO 400MHz; δ) 10.75 (1H,s,NH) 8.55 (1H,s,NH^+) 8.18 (1H,s,NH^+) 8.28 (1H,d,aromatic CH) 7.73 (1H,dd, aromatic CH) 7.50 (1H,s,thiazole CH) 7.32-7.41 (1H,m,aromatic CH) 4.12 (2H,d,OCH_2) 3.26 (2H,d,equatorial CH_2N) 2.80-2.92 (2H,m,axial CH_2N) 2.77-2.80 (2H,m,CH_2) 1.90-2.02 (1H,m,CH of piperidine ring) 1.82 (2H,d,equatorial CH_2 of piperidine ring) 1.30-1.41 (2H,m,axial CH_2 of piperidine ring) 1.32 (3H,t, CH_3)

Example 43

Piperidine-4-ylmethyl(2-{4-ethyl-1,3-thiazol-2-yl}4-hydroxy)phenylcarbamate hydrochloride

To a solution of tert-butyl-4-({[({2-[4-ethyl-1,3-thiazol-2-yl]-4-hydroxy}phenyl)amino]oxy}methyl)-piperidine-1-carboxylate (100mg) in methanol (2.5ml) 1M HCl in 1,4-dioxane was added (2.5ml). The reaction mixture was stirred for 1 hour at room temperature then evaporated to give the title compound as a pale yellow solid (81mg).

LC/MS ESI R_T 2.72mins MH^+ 362

NMR (d^6 DMSO 400MHz; δ) 10.52 (1H,s,NH) 9.84 (1H,s,OH) 8.73 (1H,s,NH^+) 8.34 (1H,s,NH^+) 7.88 (1H,s,aromatic CH) 7.41 (1H,s, thiazole CH) 7.28 (1H,s, aromatic CH) 7.88 (1H,d, aromatic CH) 3.96 (2H,d,OCH_2) 3.28 (2H,d,equatorial CH_2N) 2.80-2.92 (2H,m,axial CH_2N) 2.73-2.84 (2H,m,CH_2) 1.94 (1H,s, CH of piperidine ring) 1.82 (2H,d,equatorial CH_2 of piperidine ring) 1.32-1.45 (2H,m,axial CH_2 of piperidine ring) 1.31 (3H,t,CH_3)

Example 49

(1-Butylpiperidin-4-yl)methyl 2-(4-methyl-1,3-thiazol-2-yl)phenyl]carbamate hydrochloride

Piperidin-4-ylmethyl 2-(4-methyl-1,3-thiazol-2-yl) phenylcarbamate (200mg) dissolved in methanol (8ml) at room temperature. Butyraldehyde (0.18ml) was added and the solution was stirred for 24 hours at room temperature. A solution of sodium borohydride (25mg) in water (0.5ml) was added and stirred for 30 minutes. Further water was added (5ml) and mixture acidified with 2N Hydrochloric acid to pH1, neutralised with 8% aqueous sodium bicarbonate solution and extracted with ethyl acetate (x3). The combined organic extracts were dried ($MgSO_4$) and solvent evaporated. The residue purified by column chromatography on silica. Elution with dichloromethane / methanol (2%) and salt formation with 1.0 M HCl solution in diethyl ether gave the title compound as a yellow solid (20mg)

LC/MS ESI R_T 2.79mins MH^+ 388

NMR (MeOH-*d*4 400 MHz;δ) 7.95 (1H,d,CH aromatic) 7.7 (1H,d,CH aromatic) 7.4 (1H,t,CH aromatic) 7.3 (1H,s,CH thiazole) 7.15 (1H,t,CH aromatic) 4.0(2H,d,OCH_2) 3.55(2H,d, CH_2 piperidine) 3.0(2H,t, CH_2) 2.9(2H,t, CH_2 piperidine) 2.45(3H,s,CH_3) 1.95(3H,bd,CH + CH_2 piperidine) 1.65(2H,m,CH_2) 1.55(2H,q,CH_2 piperidine) 1.35(2H,m,CH_2) 0.9(3H,t,CH_3)

Example 50

[1-{2-[(Methylsulphonyl)amino]ethyl}piperidin-4-yl)methyl 2-(4-methyl-1,3- thiazol-2-yl)phenylcarbamate hydrochloride

Triphosgene (94mg) dissolved in dry tetrahydrofuran (10ml) at room temperature and solution stirred under nitrogen. This was cooled to 0°C and a solution of N-[2-[4-(Hydroxymethyl)-1-piperidinyl]ethyl]sulphonamide (190mg) with N,N-Diisopropylethylamine (0.14ml) was added. Stirred for 1 hour at 0°C. A solution of 2-(4-methyl-1,3-thiazol-2-yl)aniline (150mg) in dry tetrahydrofuran (4ml) added and allowed the temperature of reaction to reach room temperature. Stirred for 24 hours. Filtered and the filtrate concentrated to a yellow oil. Purified by column chromatography on silica, eluted with dichloromethane / methanol (2%) increasing to dichloromethane / methanol (5%). Salt formation with 1.0 M HCl solution in diethyl ether gave the title compound as a yellow solid (27mg)

LC/MS ESI R_T 2.87mins MH^+ 453

NMR (MeOH-*d*4 400 MHz;δ) 8.2(1H,d,CH aromatic) 7.85(1H,d,CH aromatic) 7.5(1H,t,CH aromatic) 7.35(1H,s,CH thiazole) 7.2(1H,t,CH aromatic) 4.15(2H,d,OCH_2) 3.75(2H,d,CH_2 piperidine) 3.55(2H,t,CH_2) 3.35(2H,t,CH_2) 3.1(2H,t,CH_2 piperidine) 3.05(3H,s,CH_3) 2.65(3H,s,CH_3) 2.1(3H,m,CH_2 + CH piperidine) 1.7(2H,q,CH_2 piperidine)

Example 51

(4-Fluoropiperidin-4-yl)methyl 2-(4-methyl-1,3-thiazol-2-yl)phenylcarbamate

A solution of benzyl 4-fluoro-4-[2-({[2-(4-methyl-1,3-thiazol-2-yl)phenyl]amino}oxy)-2-oxoethyl]piperidine-1-carboxylate (100mg) in ethanol was hydrogenolysed over palladium catalyst (10%; 50mg) over 2h. The catalyst was filtered off and the filtrate evaporated to give the title compound as a colourless solid (43mg)

LC/MS ESI R_T 2.55mins, MH^+ 350

NMR ($CDCl_3$ 400MHz; δ) 12.1 (1H, br s NH), 8.36 (1H, br s, aromatic CH) 7.75 (1H, dd, aromatic CH) 7.40 (1H, ddd, aromatic CH) 7.09 (1H, ddd, aromatic CH) 6.90 (1H,d, aromatic CH) 4.34 (2H, d, [J 21Hz],CH_2) 3.44 (2H, br d, CH_2 EQ) 3.21

(2H, m, CH_2 AX) 2.50 (3H, s, CH_3) 2.28-2.08 (4H, m, 2xCH_2) 1.80 (3H, m, CH_2 + CH) 1.40 (2H, br q, CH_2).

Example 52

[(2alpha,6beta)-1-benzyl-2,6-dimethylpiperidin-4-yl]methyl 2-(4-methyl-1,3-thiazol-2-yl)phenylcarbamate

Triphosgene (39mg) was added to a solution of [(2alpha,6beta)-1-benzyl-2,6-dimethylpiperidin-4-yl]methanol (61mg) and diisopropylethylamine (0.1ml) in dry THF (5ml) at room temperature under nitrogen. The mixture was stirred for 2h, then a solution of 2-(4-methyl-1,3-thiazol-2-yl)aniline (50mg) in dry THF (1ml) was added dropwise and the mixture stirred for 16h. The solvent was evaporated and the residue purified by chromatography on silica. Elution with dichloromethane/ethanol/ammonia 400:8:1 gave the title compound as a colourless foam (31mg)

NMR ($CDCl_3$ 400MHz; δ) 11.90 (1H, br s NH), 8.42 (1H, br d, aromatic CH) 7.72 (1H, dd, aromatic CH) 7.41-7.18 (6H, m, aromatic 6xCH) 7.04 (1H, br t, aromatic CH) 6.85 (1H,s, aromatic CH) 4.01 (2H, d,CH_2) 3.93,3.44 (2H, 2xd, CH_2) 3.02 (1H, m, CH) 2.88 (1H, m, CH) 2.52δ (3H, s, CH_3) 2.14 (1H, m, CH) 1.70 (1H, br d, CH EQ) 1.55-1.46 (2H,m,CH_2) 1.15 (1H,t, CH AX) 1.09 (3H,d,CH_3) 1.00 (3H,d,CH_3).

LC/MS ESI R_T 2.94mins MH^+ 450

Example 53

[(2α,6β)-2,6-Dimethylpiperidin-4-yl]methyl 2-(4-methyl-1,3-thiazol-2-yl)phenylcarbamate

A solution of [(2alpha,6beta)-1-benzyl-2,6-dimethylpiperidin-4-yl]methyl 2-(4-methyl-1,3-thiazol-2-yl)phenylcarbamate (31mg) in ethanol (10ml) was hydrogenolysed over palladium oxide (10% on carbon;10mg) for 16h. The catalyst was filtered off and the filtrate evaporated to give the title compound as a mixture of enantiomers (2mg)

LC/MS ESI R_T 2.81mins MH^+ 360

Example 54

[(2alpha,6beta)-2,6-dimethylpiperidin-4-yl]methyl 2-(4-methyl-1,3-thiazol-2-yl)phenylcarbamate hydrochloride isomer 1

Ethereal HCl (1M;2ml) was added to a solution of tert-butyl (2R,6R)-2,6-dimethyl-4-{[({[2-(4-methyl-1,3-thiazol-2-yl)phenyl]amino}carbonyl)oxy]methyl}piperidine-1-carboxylate isomer 1 in methanol (2ml) containing dichloromethane (0.5ml) and the mixture stirred at room temperature for 18h. The solvent was evaporated to give the title compound as a colourless solid (65mg)

LC/MS ESI R_T 2.80mins MH^+ 360

Sample resolved on CHIRALCEL OD-H

Manufacturer DIACEL CHEMICAL INDUSTRIES LTD

Column size 0.46cm I.D. x 25cm

Column no. ODHOCE-IF029

Eluent 10% Ethanol/Heptane

Flowrate 1ml/min

Temp. RT

Wavelength 215nm

Injection volume 15ul

Retention time 10.69 mins

Example 55

[(2alpha,6beta)-2,6-dimethylpiperidin-4-yl]methyl 2-(4-methyl-1,3-thiazol-2-yl)phenylcarbamate hydrochloride isomer 2

Ethereal HCl (1M;2ml) was added to a solution of tert-butyl (2S,6S)-2,6-dimethyl-4-{[({[2-(4-methyl-1,3-thiazol-2-yl)phenyl]amino}carbonyl)oxy]methyl}piperidine-1-carboxylate isomer 2 (40mg)

in methanol (2ml) containing dichloromethane (0.5ml) and the mixture stirred at room temperature for 18h. The solvent was evaporated to give the title compound as a colourless solid (37mg)

LC/MS ESI R_T 2.81mins MH^+ 360

5048-Sample resolved on CHIRALCEL OD-H

Manufacturer DIACEL CHEMICAL INDUSTRIES LTD

Column size 0.46cm I.D. x 25cm

Column no. ODHOCE-IF029

Eluent 10% Ethanol/Heptane

Flowrate 1ml/min

Temp. RT

Wavelength 215nm

Injection volume 15ul

Retention time = 12.21 mins

Example 56

[(2alpha,4beta,6alpha)-1-benzyl-2,6-dimethylpiperidin-4-yl]methyl 2-(4-methyl-1,3-thiazol-2-yl)phenylcarbamate isomer 1

Triphosgene (64mg) was added to a solution of [(2alpha,4beta,6alpha)-1-benzyl-2,6-dimethylpiperidin-4-yl]methanol isomer 2 (100mg) and diisopropylethylamine (0.15ml) in dry THF (5ml) at room temperature under nitrogen. The mixture was stirred for 2h, then a solution of 2-(4-methyl-1,3-thiazol-2-yl)aniline (81mg) in dry THF (1ml) was added dropwise and the mixture stirred for 16h. The yellow suspension was partitioned betweem water (10ml) and ethyl acetate (3x10ml) and the combined organic extracts dried (MgSO4). The solvent was evaporated and the residue purified by chromatography on silica. Elution with dichloromethane/ethanol/ammonia 400:8:1 gave the title compound as a colourless solid (61mg)

LCMS ESI R_T 3.04mins MH^+ 450

Tlc SiO_2 (Dichloromethane / ethanol / ammonia 200:8:1) R_f 0.2

Example 57

[(2alpha,4alpha,6alpha)-1-benzyl-2,6-dimethylpiperidin-4-yl]methyl 2-(4-methyl-1,3-thiazol-2-yl)phenylcarbamate isomer 2

Triphosgene (43mg) was added to a solution of [(2alpha,4alpha,6alpha)-1-benzyl-2,6-dimethylpiperidin-4-yl]methanol isomer 2 (B) (67mg) and diisopropylethylamine (0.10ml) in dry THF (5ml) at room temperature under nitrogen. The mixture was stirred for 2h, then a solution of 2-(4-methyl-1,3-thiazol-2-yl)aniline (54mg) in dry THF (1ml) was added dropwise and the mixture stirred for 16h. The yellow suspension was partitioned between water (10ml) and ethyl acetate (3x10ml) and the combined organic extracts dried ($MgSO_4$). The solvent was evaporated and the residue purified by

chromatography on silica. Elution with dichloromethane/ethanol/ammonia 300:8:1 gave the title compound as a colourless solid (76mg)

LC/MS ESI R_T 3.07mins MH^+ 450

Tlc SiO_2 (Dichloromethane / ethanol / ammonia 200:8:1) R_f 0.18

Example 58

[(2alpha,4beta,6alpha)-2,6-dimethylpiperidin-4-yl]methyl 2-(4-methyl-1,3-thiazol-2-yl)phenylcarbamate isomer 2

A solution of [(2alpha,4beta,6alpha)-1-benzyl-2,6-dimethylpiperidin-4-yl]methyl 2-(4-methyl-1,3-thiazol-2-yl)phenylcarbamate isomer 1 (61mg) in ethanol (4ml) was hydrogenolysed over palladium (10mg) for 16h. The catalyst was filtered off and the filtrate evaporated to give the title compound as a colourless solid (43.8mg)

LC/MS ESI R_T 2.80mins MH^+ 360

NMR ($CDCl_3$ / MeOD 400MHz; δ) 8.37 (1H, br d,aromatic CH), 7.74 (1H, dd, aromatic CH) 7.39 (1H, ddd, aromatic CH) 7.08 (1H, ddd, aromatic CH) 6.90 (1H, s, aromatic CH) 4.28 (2H,d,CH_2) 3.30 (2H, m,2xCH) 2.51 (3H, s, CH_3) 2.00-1.85 (4H, m, 2xCH_2) 1.47 (6H, d, 2xCH_3)

Example 59

[(2alpha,4alpha,6alpha)-2,6-dimethylpiperidin-4-yl]methyl 2-(4-methyl-1,3-thiazol-2-yl)phenylcarbamate isomer 1

A solution of [(2alpha,4alpha,6alpha)-1-benzyl-2,6-dimethylpiperidin-4-yl]methyl 2-(4-methyl-1,3-thiazol-2-yl)phenylcarbamate isomer 2 (76mg) in ethanol (4ml) was hydrogenolysed over palladium (10mg) for 16h. The catalyst was filtered off and the filtrate evaporated. The residue was purified by chromatography on silica. Elution with dichloromethane / ethanol / ammonia 100:8:1 gave the title compound as a colourless solid (23.5mg)

LC/MS ESI R_T 2.77mins MH^+ 360

NMR ($CDCl_3$ 400MHz; δ) 11.80 (1H, br s, NH) 8.42 (1H, br d,aromatic CH), 7.72 (1H, dd, aromatic CH) 7.38 (1H, ddd, aromatic CH) 7.04 (1H, ddd, aromatic CH) 6.86 (1H, br s, aromatic CH) 4.02 (2H,d,CH_2) 2.73 (2H, m,2xCH) 2.52 (3H, s, CH_3)

1.91 (1H, m, CH) 1.76 (2H, br d, CH_2 EQ) 1.10 (6H, d, 2xCH_3) 0.82 (2H, br q, CH_2 AX)

Intermediate 131

tert-Butyl 4-{[({[4-(4,4,5,5-tetrametyl-[1,3,2]dioxaborolan-2-yl) phenyl]amino}carbonyl)oxy]methyl}piperidine-1-carboxylate

A mixture of tert-butyl 4-(hydroxymethyl)piperidine-1-carboxylate (147.5mg) and diisopropylethylamine (0.119ml) in dry THF (1.5ml) was added dropwise to a solution of triphosgene (67mg) in dry THF (1.5ml) at 0-5°C under nitrogen. The mixture was stirred for 1.5h, then a solution of 4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenylamine (150mg) in dry THF(1.5ml) was added dropwise. The mixture was stirred for 16h at room temperature. Water (10ml) followed with ethyl acetate (5ml) were added to the reaction. The aqueous phase was extracted with ethyl acetate (5ml). The combined organics were washed with brine (10ml) and dried (Na_2SO_4). The solvent was evaporated and the residue purified by Biotage Flash™ on silica. Elution with dichloromethane followed by ethylacetate gave the title compound as a pale yellow powder (280mg)

LC/MS ESI R_T 2.69mins M^+ 460.4

Tlc SiO_2 (1:1 Hexane: Ethyl Acetate) Rf 0.75

Intermediate 132

tert-Butyl 4-{[({[3-(4,4,5,5-tetrametyl-[1,3,2]dioxaborolan-2-yl) phenyl]amino}carbonyl)oxy]methyl}piperidine-1-carboxylate

A mixture of tert-butyl 4-(hydroxymethyl)piperidine-1-carboxylate (235mg) and diisopropylethylamine (0.19ml) in dry THF (1.5ml) was added dropwise to a solution of triphosgene (108mg) in dry THF (2.0ml) at 0-5°C under nitrogen. The mixture was stirred for 1.5h, then a solution of 3-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenylamine (239mg) in dry THF(1.5ml) was added dropwise. The mixture was stirred for 16h at room temperature. Water (10ml) followed with ethyl acetate (5ml) were added to the reaction. The aqueous phase was extracted with ethyl acetate (5ml). The combined organics were washed with brine (10ml) and dried (Na_2SO_4). The solvent was evaporated and the residue purified by Biotage Flash™ on silica. Elution

with dichloromethane followed by ethylacetate gave the title compound as a pale yellow powder (501mg)

LC/MS ESI R_T 2.61mins M^+ 460.4

Tlc SiO_2 (1:1 Hexane: Ethyl Acetate) Rf 0.73

Example 60

tert-Butyl 4-{[({[4-(4-chloro-1,3-thiazol-2-yl) phenyl]amino}carbonyl)oxy]methyl}piperidine-1-carboxylate

A mixture of tert-Butyl 4-{[({[4-(4,4,5,5-tetrametyl-[1,3,2]dioxaborolan-2-yl) phenyl]amino}carbonyl)oxy]methyl}piperidine-1-carboxylate (400mg) and 2,4-dichloro-1,3-thaizol (134mg) were dissovled in ethylene glycol dimethyl ether (8ml) and 2M sodium bicarbanate in water (3ml). Nitrogen was bubbled through for more than 10mins before tetrakis(triphenyl phosphine) palladium (0) (201mg)was added in one portion. The reaction mixture was heated at 80 degree for 10 hours. Water (15ml) followed with ethyl acetate (20ml) were added to the reaction. The aqueous phase was extracted with ethyl acetate (15ml). The combined organics were washed with brine (10ml) and dried (Na_2SO_4). The solvent was evaporated and the residue purified by Biotage Flash™ on silica. Elution with dichloromethane followed by ethylacetate gave the title compound as a pale yellow powder (160mg)

LC/MS ESI R_T 2.75mins M^+ 452.2

Example 61

tert-Butyl 4-{[({[3-(4-chloro-1,3-thiazol-2-yl) phenyl]amino}carbonyl)oxy]methyl}piperidine-1-carboxylate

A mixture of tert-Butyl 4-{[({[3-(4,4,5,5-tetrametyl-[1,3,2]dioxaborolan-2-yl) phenyl]amino}carbonyl)oxy]methyl}piperidine-1-carboxylate (500mg) and 2,4-dichloro-1,3-thaizol (168mg) were dissovled in ethylene glycol dimethyl ether (16ml) and 2M sodium bicarbanate in water (8ml). Nitrogen was bubbled through for more than 10mins before tetrakis(triphenyl phosphine) palladium (0) (251mg)was added in one portion. The reaction mixture was heated at 80 degree for 10 hours. Water (15ml) followed with ethyl acetate (20ml) were added to the reaction. The aqueous phase was extracted with ethyl acetate (15ml). The combined organics were washed with brine

(10ml) and dried (Na_2SO_4). The solvent was evaporated and the residue purified by Biotage Flash™ on silica. Elution with dichloromethane followed by ethylacetate gave the title compound as a pale yellow powder (300mg)

LC/MS ESI R_T 2.77mins M^+ 452.2

Example 62

Piperidin-4-ylmethyl 4-(4-chloro-1,3-thiazol-2-yl)phenylcarbamate hydrochloride

A solution of tert-butyl 4-{[({[4-(4-chloro-1,3-thiazol-2-yl) phenyl]amino}carbonyl)oxy]methyl}piperidine-1-carboxylate (120mg) in methanol (10ml) was treated with 4M hydrogen chloride in dioxane (1ml) . The reaction mixture was stirred at room temperature for 16h. The mixture was then concentrated and the resultant residue was triturated in 5: 1, ether / ethyl acetate to give the title compound as a yellow powder (100mg)

LC/MS ESI R_T 1.58mins M^+ 352.2

Example 63

Piperidin-4-ylmethyl 3-(4-chloro-1,3-thiazol-2-yl)phenylcarbamate hydrochloride

A solution of tert-butyl 4-{[({[3-(4-chloro-1,3-thiazol-2-yl) phenyl]amino}carbonyl)oxy]methyl}piperidine-1-carboxylate (300mg) in methanol (10ml) was treated with 4M hydrogen chloride in dioxane (3ml) . The reaction mixture was stirred at room temperature for 16h. The reaction mixture was filtered and washed with methylene chloride and methanol to give the title compound as a yellow powder (110mg)

LC/MS ESI R_T 1.40mins M^+ 352.2

Example 64

1-cyclohexylmethyl-piperidin-4-ylmethyl 4-(4-chloro-1,3-thiazol-2-yl)phenylcarbamate

A solution piperidin-4-ylmethyl 4-(4-chloro-1,3-thiazol-2-yl)phenylcarbamate(30mg) in methylene chloride (10ml)was treated with cyclohexanecarbaldehyde (0.01ml) at 0 degree and stirred at 0 degree for half an hour before sodium triacetoxyborohydride (27mg) was added in one portion. The reaction mixture was allowed to warm to room temperature slowly and stirred overnight. Methylene chloride (10ml) was added to the

reaction followed by satd $NaHCO_3$ (aq) (10ml). The aqueous phase was extracted with ethyl acetate (15ml_x 3). The combined organics were washed with brine (10ml) and dried (Na_2SO_4)._The solvent was evaporated to give the title compound as a white powder (21mg).

LC/MS ESI R_T 1.73mins M^+ 448.2

Example 65

1-cyclohexylmethyl-piperidin-4-ylmethyl 3-(4-chloro-1,3-thiazol-2-yl)phenylcarbamate

A solution piperidin-4-ylmethyl 3-(4-chloro-1,3-thiazol-2-yl)phenylcarbamate(60mg) in methylene chloride (20ml)was treated with cyclohexanecarbaldehyde (0.01ml) at 0 degree and stirred at 0 degree for half an hour before sodium triacetoxyborohydride (27mg) was added in one portion. The reaction mixture was allowed to warm to room temperature slowly and stirred overnight. Methylene chloride (10ml) was added to the reaction followed by satd $NaHCO_3$ (aq) (10ml). The aqueous phase was extracted with ethyl acetate (15ml_x 3). The combined organics were washed with brine (10ml) and dried (Na_2SO_4)._The solvent was evaporated to give the title compound as a white powder (41mg).

LC/MS ESI R_T 1.97mins M^+ 448.2

Example 66

4-[4-(4-Chloro-thiazol-2-yl)-phenylcarbamoyloxymethyl]-1-cyclohexylmethyl-1-methyl-piperidinium iodide

1-cyclohexylmethyl-piperidin-4-ylmethyl 4-(4-chloro-1,3-thiazol-2-yl)phenylcarbamate (20mg) was dissolved in a mixture of methanol (5ml) and methylene chloride (10ml). Methyl iodide(1ml) was added at room temperature followed by $NaCO_3$ (50mg). The reaction mixture was filtered through a pad of celite after stirring overnight at room temperature to afford the title compound as a white powder (13mg).

LC/MS ESI R_T 1.82mins M^+ 462.4

Example 67

4-[3-(4-Chloro-thiazol-2-yl)-phenylcarbamoyloxymethyl]-1-cyclohexylmethyl-1-methyl-piperidinium iodide

1-cyclohexylmethyl-piperidin-4-ylmethyl 3-(4-chloro-1,3-thiazol-2-yl)phenylcarbamate (18mg) was dissolved in a mixture of methanol (5ml) and methylene chloride (10ml). Methyl iodide(1ml) was added at room temperature followed by $NaCO_3$ (50mg). The reaction mixture was filtered through a pad of celite after stirring overnight at room temperature to afford the title compound as a white powder (10mg).

LC/MS ESI R_T 1.95mins M^+ 462.4

Example 68

4-[4-(4-Chloro-thiazol-2-yl)-phenylcarbamoyloxymethyl]-1,1-dimethyl-piperidinium

A solution piperidin-4-ylmethyl 4-(4-chloro-1,3-thiazol-2-yl)phenylcarbamate(20mg) in methylene chloride (10ml) and methanal (5ml) was treated with methyl iodide(1ml) at room temperature followed by $NaCO_3$ (50mg). The reaction mixture was filtered through a pad of celite after stirring overnight at room temperature to afford the title compound as a white powder (11mg).

LC/MS ESI R_T 1.48mins M^+ 380.2

Example 69

4-[3-(4-Chloro-thiazol-2-yl)-phenylcarbamoyloxymethyl]-1,1-dimethyl-piperidinium

A solution piperidin-4-ylmethyl 3-(4-chloro-1,3-thiazol-2-yl)phenylcarbamate(40mg) in methylene chloride (10ml) and methanal (5ml) was treated with methyl iodide(1ml) at room temperature followed by $NaCO_3$ (50mg). The reaction mixture was filtered through a pad of celite after stirring overnight at room temperature to afford the title compound as a white powder (17mg).

LC/MS ESI R_T 1.55mins M^+ 380.4

BIOLOGICAL EXAMPLES

The inhibitory effects of compounds at the M_3 mAChR of the present invention are determined by the following *in vitro* and *in vivo* functional assays:

Analysis of Inhibition of Receptor Activation by Calcium Mobilization:

Stimulation of mAChRs expressed on CHO cells were analyzed by monitoring receptor-activated calcium mobilization as previously described(4). CHO cells stably expressing M_3 mAChRs were plated in 96 well black wall/clear bottom plates. After 18 to 24 hours, media was aspirated and replaced with 100 µl of load media (EMEM with Earl's salts, 0.1% RIA-grade BSA (Sigma, St. Louis MO), and 4 µM Fluo-3-acetoxymethyl ester fluorescent indicator dye (Fluo-3 AM, Molecular Probes, Eugene, OR) and incubated 1 hr at 37° C. The dye-containing media was then aspirated, replaced with fresh media (without Fluo-3 AM), and cells were incubated for 10 minutes at 37° C. Cells were then washed 3 times and incubated for 10 minutes at 37° C in 100 µl of assay buffer (0.1% gelatin (Sigma), 120 mM NaCl, 4.6 mM KCl, 1 mM KH_2PO_4, 25 mM $NaHCO_3$, 1.0 mM $CaCl_2$, 1.1 mM $MgCl_2$, 11 mM glucose, 20mM HEPES (pH 7.4)). 50 µl of compound ($1x10^{-11}$ – $1x10^{-5}$ M final in the assay) was added and the plates were incubated for 10 min. at 37° C. Plates were then placed into a fluorescent light intensity plate reader (FLIPR, Molecular Probes) where the dye loaded cells were exposed to excitation light (488 nm) from a 6 watt argon laser. Cells were activated by adding 50 µl of acetylcholine (0.1-10 nM final), prepared in buffer containing 0.1% BSA, at a rate of 50 µl/sec. Calcium mobilization, monitored as change in cytosolic calcium concentration, was measured as change in 566 nm emission intensity. The change in emission intensity is directly related to cytosolic calcium levels (5). The emitted fluorescence from all 96 wells is measured simultaneously using a cooled CCD camera. Data points are collected every second. This data was then plotting and analyzed using GraphPad PRISM software.

Methacholine-induced bronchoconstriction

Airway responsiveness to methacholine was determined in awake, unrestrained BalbC mice (n = 6 each group). Barometric plethysmography was used to measure enhanced pause (Penh), a unitless measure that has been shown to correlate with the changes in airway resistance that occur during bronchial challenge with methacholine(2). Mice were pretreated with 50 µl of compound (0.003-10 µg/mouse) in 50 µl of vehicle (10% DMSO) intranasally, i.v., i.p. or p.o, and were then placed in the plethysmography chamber. Once in the chamber, the mice were allowed to

equilibrate for 10 min before taking a baseline Penh measurement for 5 minutes. Mice were then challenged with an aerosol of methacholine (10 mg/ml) for 2 minutes. Penh was recorded continuously for 7 min starting at the inception of the methacholine aerosol, and continuing for 5 minutes afterward. Data for each mouse were analyzed and plotted by using GraphPad PRISM software.

The present compounds are useful for treating a variety of indications, including but not limited to respiratory-tract disorders such as chronic obstructive lung disease, chronic bronchitis, asthma, chronic respiratory obstruction, pulmonary fibrosis, pulmonary emphysema, and allergic rhinitis; gastrointestinal-tract disorders such as irritable bowel syndrome, spasmodic colitis, gastroduodenal ulcers, gastrointestinal convulsions or hyperanakinesia, diverticulitis, pain accompanying spasms of gastrointestinal smooth musculature; urinary-tract disorders accompanying micturition disorders including neurogenic pollakisuria, neurogenic bladder, nocturnal enuresis, psychosomatic bladder, incontinence associated with bladder spasms or chronic cystitis, urinary urgency or pollakiuria, and motion sickness.

Methods of administering the present compounds will be readily apparent to the skilled artisan.

Dry powder compositions for topical delivery to the lung by inhalation may, for example, be presented in capsules and cartridges of for example gelatine, or blisters of for example laminated aluminium foil, for use in an inhaler or insufflator. Formulations generally contain a powder mix for inhalation of the compound of the invention and a suitable powder base (carrier substance) such as lactose or starch. Use of lactose is preferred. Each capsule or cartridge may generally contain between 20µg-10mg of the compound of formula (I) optionally in combination with another therapeutically active ingredient. Alternatively, the compound of the invention may be presented without excipients.

Suitably, the medicament dispenser is of a type selected from the group consisting of a reservoir dry powder inhaler (RDPI), a multi-dose dry powder inhaler (MDPI), and a metered dose inhaler (MDI).

By reservoir dry powder inhaler (RDPI) it is meant an inhaler having a reservoir form pack suitable for comprising multiple (un-metered doses) of medicament in dry powder form and including means for metering medicament dose from the reservoir to

a delivery position. The metering means may for example comprise a metering cup, which is movable from a first position where the cup may be filled with medicament from the reservoir to a second position where the metered medicament dose is made available to the patient for inhalation.

By multi-dose dry powder inhaler (MDPI) is meant an inhaler suitable for dispensing medicament in dry powder form, wherein the medicament is comprised within a multi-dose pack containing (or otherwise carrying) multiple, define doses (or parts thereof) of medicament. In a preferred aspect, the carrier has a blister pack form, but it could also, for example, comprise a capsule-based pack form or a carrier onto which medicament has been applied by any suitable process including printing, painting and vacuum occlusion.

The formulation can be pre-metered (eg as in Diskus, see GB 2242134 or Diskhaler, see GB 2178965, 2129691 and 2169265) or metered in use (eg as in Turbuhaler, see EP 69715). An example of a unit-dose device is Rotahaler (see GB 2064336). The Diskus inhalation device comprises an elongate strip formed from a base sheet having a plurality of recesses spaced along its length and a lid sheet hermetically but peelably sealed thereto to define a plurality of containers, each container having therein an inhalable formulation containing a compound of formula (I) preferably combined with lactose. Preferably, the strip is sufficiently flexible to be wound into a roll. The lid sheet and base sheet will preferably have leading end portions which are not sealed to one another and at least one of the said leading end portions is constructed to be attached to a winding means. Also, preferably the hermetic seal between the base and lid sheets extends over their whole width. The lid sheet may preferably be peeled from the base sheet in a longitudinal direction from a first end of the said base sheet.

In one aspect, the multi-dose pack is a blister pack comprising multiple blisters for containment of medicament in dry powder form. The blisters are typically arranged in regular fashion for ease of release of medicament therefrom.

In one aspect, the multi-dose blister pack comprises plural blisters arranged in generally circular fashion on a disc-form blister pack. In another aspect, the multi-dose blister pack is elongate in form, for example comprising a strip or a tape.

Preferably, the multi-dose blister pack is defined between two members peelably secured to one another. US Patents Nos. 5,860,419, 5,873,360 and 5,590,645 describe medicament packs of this general type. In this aspect, the device is usually provided with an opening station comprising peeling means for peeling the members apart to access each medicament dose. Suitably, the device is adapted for use where the peelable members are elongate sheets which define a plurality of medicament containers spaced along the length thereof, the device being provided with indexing means for indexing each container in turn. More preferably, the device is adapted for use where one of the sheets is a base sheet having a plurality of pockets therein, and the other of the sheets is a lid sheet, each pocket and the adjacent part of the lid sheet defining a respective one of the containers, the device comprising driving means for pulling the lid sheet and base sheet apart at the opening station.

By metered dose inhaler (MDI) it is meant a medicament dispenser suitable for dispensing medicament in aerosol form, wherein the medicament is comprised in an aerosol container suitable for containing a propellant-based aerosol medicament formulation. The aerosol container is typically provided with a metering valve, for example a slide valve, for release of the aerosol form medicament formulation to the patient. The aerosol container is generally designed to deliver a predetermined dose of medicament upon each actuation by means of the valve, which can be opened either by depressing the valve while the container is held stationary or by depressing the container while the valve is held stationary.

Where the medicament container is an aerosol container, the valve typically comprises a valve body having an inlet port through which a medicament aerosol formulation may enter said valve body, an outlet port through which the aerosol may exit the valve body and an open/close mechanism by means of which flow through said outlet port is controllable.

The valve may be a slide valve wherein the open/close mechanism comprises a sealing ring and receivable by the sealing ring a valve stem having a dispensing passage, the valve stem being slidably movable within the ring from a valve-closed to a valve-open position in which the interior of the valve body is in communication with the exterior of the valve body via the dispensing passage.

Typically, the valve is a metering valve. The metering volumes are typically from 10 to 100 µl, such as 25 µl, 50 µl or 63 µl. Suitably, the valve body defines a metering chamber for metering an amount of medicament formulation and an open/close mechanism by means of which the flow through the inlet port to the metering chamber is controllable. Preferably, the valve body has a sampling chamber in communication with the metering chamber via a second inlet port, said inlet port being controllable by means of an open/close mechanism thereby regulating the flow of medicament formulation into the metering chamber.

The valve may also comprise a 'free flow aerosol valve' having a chamber and a valve stem extending into the chamber and movable relative to the chamber between dispensing and non-dispensing positions. The valve stem has a configuration and the chamber has an internal configuration such that a metered volume is defined therebetween and such that during movement between is non-dispensing and dispensing positions the valve stem sequentially: (i) allows free flow of aerosol formulation into the chamber, (ii) defines a closed metered volume for pressurized aerosol formulation between the external surface of the valve stem and internal surface of the chamber, and (iii) moves with the closed metered volume within the chamber without decreasing the volume of the closed metered volume until the metered volume communicates with an outlet passage thereby allowing dispensing of the metered volume of pressurized aerosol formulation. A valve of this type is described in U.S. Patent No. 5,772,085. Additionally, intra-nasal delivery of the present compounds is effective.

To formulate an effective pharmaceutical nasal composition, the medicament must be delivered readily to all portions of the nasal cavities (the target tissues) where it performs its pharmacological function. Additionally, the medicament should remain in contact with the target tissues for relatively long periods of time. The longer the medicament remains in contact with the target tissues, the medicament must be capable of resisting those forces in the nasal passages that function to remove particles from the nose. Such forces, referred to as 'mucociliary clearance', are recognised as being extremely effective in removing particles from the nose in a rapid manner, for example, within 10-30 minutes from the time the particles enter the nose.

Other desired characteristics of a nasal composition are that it must not contain ingredients which cause the user discomfort, that it has satisfactory stability and shelf-life properties, and that it does not include constituents that are considered to be detrimental to the environment, for example ozone depletors.

A suitable dosing regime for the formulation of the present invention when administered to the nose would be for the patient to inhale deeply subsequent to the nasal cavity being cleared. During inhalation the formulation would be applied to one nostril while the other is manually compressed. This procedure would then be repeated for the other nostril.

A preferable means for applying the formulation of the present invention to the nasal passages is by use of a pre-compression pump. Most preferably, the pre-compression pump will be a VP7 model manufactured by Valois SA. Such a pump is beneficial as it will ensure that the formulation is not released until a sufficient force has been applied, otherwise smaller doses may be applied. Another advantage of the pre-compression pump is that atomisation of the spray is ensured as it will not release the formulation until the threshold pressure for effectively atomising the spray has been achieved. Typically, the VP7 model may be used with a bottle capable of holding 10-50ml of a formulation. Each spray will typically deliver 50-100µl of such a formulation, therefore, the VP7 model is capable of providing at least 100 metered doses.

Examples of Nasal Formulations

Example 1 : Nasal formulation containing active

A formulation for intranasal delivery was prepared with ingredients as follows:

	to 100%
Active	0.1% w/w
Polysorbate 80	0.025% w/w
Avicel RC591	1.5% w/w
Dextrose	5.0% w/w
BKC	0.015% w/w
EDTA	0.015% w/w
water	to 100%

in a total amount suitable for 120 actuations and the formulation was filled into a bottle fitted with a metering valve adapted to dispense 50 or 100 µl per actuation.
The device was fitted into a nasal actuator (Valois).

Example 2 : Nasal formulation containing active

A formulation for intranasal delivery was prepared with ingredients as follows:

Active	0.005% w/w
Tyloxapol	2% w/w
dextrose	5% w/w
BKC	0.015% w/w
EDTA	0.015% w/w
water	to 100%

in a total amount suitable for 120 actuations and the formulation was filled into a bottle (plastic or glass) fitted with a metering valve adapted to dispense 50 or 100 µl per actuation

The device was fitted into a nasal actuator (Valois, e.g. VP3, VP7 or VP7D)

Example 3 : Nasal formulation containing active

A formulation for intranasal delivery was prepared with ingredients as follows:

active	0.05% w/w
Triton X-100	5% w/w
Dextrose	4% w/w
BKC	0.015% w/w
EDTA	0.015% w/w
water	to 100%

in a total amount suitable for 120 actuations and the formulation was filled into a bottle fitted with a metering valve adapted to dispense 50 or 100 µl per actuation.

Example 4 : Nasal formulation containing active

A formulation for intranasal delivery was prepared with ingredients as follows:

active	0.05% w/w
Tyloxapol	5% w/w

dextrose	5% w/w
BKC	0.015% w/w
EDTA	0.015% w/w
water	to 100%

in a total amount suitable for 120 actuations and the formulation was filled into a bottle fitted with a metering valve adapted to dispense 50 or 100 µl per actuation
The device was fitted into a nasal actuator (Valois).

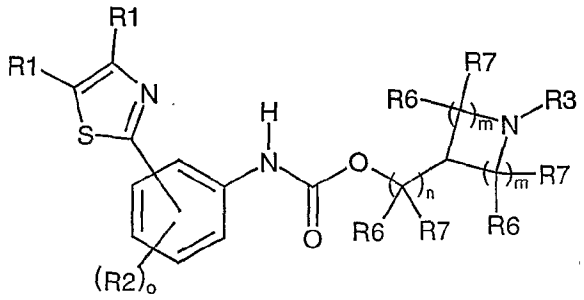
Throughout the specification and the claims which follow, unless the context requires otherwise, the word 'comprise', and variations such as 'comprises' and 'comprising', will be understood to imply the inclusion of a stated integer or step or group of integers but not to the exclusion of any other integer or step or group of integers or steps.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

The above description fully discloses the invention including preferred embodiments thereof. Modifications and improvements of the embodiments specifically disclosed herein are within the scope of the following claims. Without further elaboration, it is believed that one skilled in the are can, using the preceding description, utilize the present invention to its fullest extent. Therefore the Examples herein are to be construed as merely illustrative and not a limitation of the scope of the present invention in any way. The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows.

What is Claimed Is:

1. A compound according to the formula:



(I)

wherein:

the thiazole is ortho to the nitrogen;

R1 is selected from the group consisting of halogen, C_{1-5}alkyl, CH_2F, CHF_2;

R2 is selected from the group consisting of hydrogen, C_{1-5}alkyl, aryl, halogen, hydroxy and alkoxy;

R3 is selected from the group consisting of hydrogen, C_{1-5}alkyl, cycloalkyl, cycloalkyl C_{1-5} alkyl, C_{2-4}alkenyl, C_{2-4}alkenylaryl; cycloalkyl C_{1-5} alkyl, and C_{1-4}alkylaryl, which may be optionally substituted independently by a substituent selected from the group consisting of halogen, nitro, halosubstituted C_{1-4} alkyl, C_{1-4} alkyl, amino, mono or di-C_{1-4} alkyl substituted amine, OR_a; $C(O)R_a$, $NR_aC(O)OR_a$, $OC(O)NR_6R_7$, hydroxy, $NR_9C(O)R_a$, $S(O)_mR_a$, $C(O)NR_6R_7$, C(O)OH, $C(O)OR_a$, $S(O)_2NR_6R_7$, and $NHS(O)_2R_a$;

R_6 and R_7 are selected from the group consisting of hydrogen, and C_{1-4} alkyl, or R_6 and R_7 together form a 5 to 7 member ring which ring may optionally contain an additional heteroatom selected from oxygen, nitrogen or sulfur, and which ring may be optionally substituted;

n is 1 or 2; and independently

m is 1 or 2.

2. A compound according to claim 1 wherein:

the thiazole is ortho to the nitrogen;

R1 is selected from the group consisting of halogen, C_{1-5}alkyl, CH_2F, CHF_2;

R2 is selected from the group consisting of hydrogen, C_{1-5}alkyl, aryl, halogen, hydroxy and alkoxy;

R3 is selected from the group consisting of hydrogen, C_{1-5}alkyl, cycloalkyl, cycloalkyl C_{1-5} alkyl, C_{2-4}alkenyl, C_{2-4}alkenylaryl; cycloalkyl C_{1-5} alkyl, and C_{1-4}alkylaryl, which may be optionally substituted independently by a substituent selected from the group consisting of halogen, nitro, halosubstituted C_{1-4} alkyl, C_{1-4} alkyl, amino, mono or di-C_{1-4} alkyl substituted amine, OR_a; $C(O)R_a$, $NR_aC(O)OR_a$, $OC(O)NR_6R_7$, hydroxy, $NR_9C(O)R_a$, $S(O)_mR_a$, $C(O)NR_6R_7$, C(O)OH, $C(O)OR_a$, $S(O)_2NR_6R_7$, and $NHS(O)_2R_a$;

R_6 and R_7 are selected from the group consisting of hydrogen, and C_{1-4} alkyl, or R_6 and R_7 together form a 5 to 7 member ring which ring may optionally contain an additional heteroatom selected from oxygen, nitrogen or sulfur, and which ring may be optionally substituted;

n is 1 or 2; and independently

m is 1 or 2.

3. A compound according to claim 2 selected from the group consisting of:

[2-(4-Methyl-thiazol-2-yl)-phenyl]-carbamic acid piperidin-4-ylmethyl ester;

[2-(4-Ethyl-thiazol-2-yl)-phenyl]-carbamic acid piperidin-4-ylmethyl ester;

{2-[4-(1,1-Difluoro-methyl)-thiazol-2-yl]-phenyl}-carbamic acid piperidin-4-ylmethyl ester;

(2-Thiazol-2-yl-phenyl)-carbamic acid piperidin-4-ylmethyl ester; compound with 2,2,2-trifluoro-acetic acid;

[2-(4-Propyl-thiazol-2-yl)-phenyl]-carbamic acid piperidin-4-ylmethyl ester;

[2-(4-Methyl-thiazol-2-yl)-phenyl]-carbamic acid (2R,6R)-2,6-dimethyl-piperidin-4-ylmethyl ester;

[2-(4-Isopropyl-thiazol-2-yl)-phenyl]-carbamic acid piperidin-4-ylmethyl ester;

[2-(4-tert-Butyl-thiazol-2-yl)-phenyl]-carbamic acid piperidin-4-ylmethyl ester;

[2-(4-Bromo-thiazol-2-yl)-phenyl]-carbamic acid piperidin-4-ylmethyl ester;

[2-(4-Chloro-thiazol-2-yl)-phenyl]-carbamic acid piperidin-4-ylmethyl ester;

[2-(4-Isobutyl-thiazol-2-yl)-phenyl]-carbamic acid piperidin-4-ylmethyl ester;

[2-(4-Cyclopropylmethyl-thiazol-2-yl)-phenyl]-carbamic acid piperidin-4-ylmethyl ester;

[2-(4-Cyclopropyl-thiazol-2-yl)-phenyl]-carbamic acid piperidin-4-ylmethyl ester;

[2-(4-Cyclobutyl-thiazol-2-yl)-phenyl]-carbamic acid piperidin-4-ylmethyl ester;

[2-(4-Trifluoromethyl-thiazol-2-yl)-phenyl]-carbamic acid piperidin-4-ylmethyl ester;

[2-(4-Fluoromethyl-thiazol-2-yl)-phenyl]-carbamic acid piperidin-4-ylmethyl ester;

{2-[4-(1,1-Difluoro-ethyl)-thiazol-2-yl]-phenyl}-carbamic acid piperidin-4-ylmethyl ester;

{2-[4-(2-Fluoro-ethyl)-thiazol-2-yl]-phenyl}-carbamic acid piperidin-4-ylmethyl ester;

{2-[4-(2,2-Difluoro-ethyl)-thiazol-2-yl]-phenyl}-carbamic acid piperidin-4-ylmethyl ester;

[2-(4-Methoxymethyl-thiazol-2-yl)-phenyl]-carbamic acid piperidin-4-ylmethyl ester;

[2-(4-Hydroxymethyl-thiazol-2-yl)-phenyl]-carbamic acid piperidin-4-ylmethyl ester;

{2-[4-(1-Hydroxy-ethyl)-thiazol-2-yl]-phenyl}-carbamic acid piperidin-4-ylmethyl ester;

{2-[4-((R)-1-Hydroxy-ethyl)-thiazol-2-yl]-phenyl}-carbamic acid piperidin-4-ylmethyl ester;

{2-[4-(2-Hydroxy-ethyl)-thiazol-2-yl]-phenyl}-carbamic acid piperidin-4-ylmethyl ester;

[2-(4-Amino-thiazol-2-yl)-phenyl]-carbamic acid piperidin-4-ylmethyl ester;

[5-Fluoro-2-(4-methyl-thiazol-2-yl)-phenyl]-carbamic acid piperidin-4-ylmethyl ester;

[2-(4-Ethyl-thiazol-2-yl)-4-hydroxy-phenyl]-carbamic acid piperidin-4-ylmethyl ester;

[2-(4-Methyl-thiazol-2-yl)-phenyl]-carbamic acid (2R,6S)-2,6-dimethyl-piperidin-4-ylmethyl ester;

[2-(4-Methyl-thiazol-2-yl)-phenyl]-carbamic acid (2R,6S)-2,6-dimethyl-piperidin-4-ylmethyl ester;

[2-(4-Methyl-thiazol-2-yl)-phenyl]-carbamic acid (2R,6S)-1-benzyl-2,6-dimethyl-piperidin-4-ylmethyl ester;

[2-(4-Methyl-thiazol-2-yl)-phenyl]-carbamic acid (2R,6S)-1-benzyl-2,6-dimethyl-piperidin-4-ylmethyl ester;

[2-(4-Methyl-thiazol-2-yl)-phenyl]-carbamic acid (2R,6R)-2,6-dimethyl-piperidin-4-ylmethyl ester;

[2-(4-Methyl-thiazol-2-yl)-phenyl]-carbamic acid (2R,6R)-2,6-dimethyl-piperidin-4-ylmethyl ester;

[2-(4-Methyl-thiazol-2-yl)-phenyl]-carbamic acid (2R,6R)-1-benzyl-2,6-dimethyl-piperidin-4-ylmethyl ester;

[2-(4-Methyl-thiazol-2-yl)-phenyl]-carbamic acid 4-fluoro-piperidin-4-ylmethyl ester;

[2-(4-Methyl-thiazol-2-yl)-phenyl]-carbamic acid 1-butyl-piperidin-4-ylmethyl ester;

[2-(4-Methyl-5-methylcarbamoyl-thiazol-2-yl)-phenyl]-carbamic acid piperidin-4-ylmethyl ester;

[2-(5-Methyl-thiazol-2-yl)-phenyl]-carbamic acid piperidin-4-ylmethyl ester;

[2-(4,5-Dimethyl-thiazol-2-yl)-phenyl]-carbamic acid piperidin-4-ylmethyl ester;

[2-(4-Acetyl-thiazol-2-yl)-phenyl]-carbamic acid piperidin-4-ylmethyl ester;

{2-[4-(2-Benzyloxy-ethyl)-thiazol-2-yl]-phenyl}-carbamic acid piperidin-4-ylmethyl ester;

[2-(4-Methylcarbamoyl-thiazol-2-yl)-phenyl]-carbamic acid piperidin-4-ylmethyl ester;

2-[2-(Piperidin-4-ylmethoxycarbonylamino)-phenyl]-thiazole-4-carboxylic acid ethyl ester;

[2-(4-Dimethylaminomethyl-thiazol-2-yl)-phenyl]-carbamic acid piperidin-4-ylmethyl ester;

[2-(4-Phenyl-thiazol-2-yl)-phenyl]-carbamic acid piperidin-4-ylmethyl ester;

[2-(4-Thiophen-3-yl-thiazol-2-yl)-phenyl]-carbamic acid piperidin-4-ylmethyl ester;

[2-(4-Ethyl-thiazol-2-yl)-4-fluoro-phenyl]-carbamic acid piperidin-4-ylmethyl ester;

tert-Butyl 4-{[({[4-(4,4,5,5-tetrametyl-[1,3,2]dioxaborolan-2-yl) phenyl]amino}carbonyl)oxy]methyl}piperidine-1-carboxylate;

tert-Butyl 4-{[({[3-(4,4,5,5-tetrametyl-[1,3,2]dioxaborolan-2-yl) phenyl]amino}carbonyl)oxy]methyl}piperidine-1-carboxylate ;

tert-Butyl 4-{[({[4-(4-chloro-1,3-thiazol-2-yl) phenyl]amino}carbonyl)oxy]methyl}piperidine-1-carboxylate;

tert-Butyl 4-{[({[3-(4-chloro-1,3-thiazol-2-yl) phenyl]amino}carbonyl)oxy]methyl}piperidine-1-carboxylate;

Piperidin-4-ylmethyl 4-(4-chloro-1,3-thiazol-2-yl)phenylcarbamate hydrochloride;

Piperidin-4-ylmethyl 3-(4-chloro-1,3-thiazol-2-yl)phenylcarbamate hydrochloride ;

1-cyclohexylmethyl-piperidin-4-ylmethyl 4-(4-chloro-1,3-thiazol-2-yl)phenylcarbamate;

1-cyclohexylmethyl-piperidin-4-ylmethyl 3-(4-chloro-1,3-thiazol-2-yl)phenylcarbamate;

4-[4-(4-Chloro-thiazol-2-yl)-phenylcarbamoyloxymethyl]-1-cyclohexylmethyl-1-methyl-piperidinium iodide;

4-[3-(4-Chloro-thiazol-2-yl)-phenylcarbamoyloxymethyl]-1-cyclohexylmethyl-1-methyl-piperidinium iodide;

4-[4-(4-Chloro-thiazol-2-yl)-phenylcarbamoyloxymethyl]-1,1-dimethyl-piperidinium; and

4-[3-(4-Chloro-thiazol-2-yl)-phenylcarbamoyloxymethyl]-1,1-dimethyl-piperidinium; or a pharmaceutically acceptable salt thereof.

4. A method according to claim 3 wherein the compound is selected from the group consisting of:

[2-(4-Bromo-thiazol-2-yl)-phenyl]-carbamic acid piperidin-4-ylmethyl ester;

[2-(4-Chloro-thiazol-2-yl)-phenyl]-carbamic acid piperidin-4-ylmethyl ester;

[2-(4-Methyl-thiazol-2-yl)-phenyl]-carbamic acid piperidin-4-ylmethyl ester;

{2-[4-(1,1-Difluoro-methyl)-thiazol-2-yl]-phenyl}-carbamic acid piperidin-4-ylmethyl ester; and

[2-(4-Fluoromethyl-thiazol-2-yl)-phenyl]-carbamic acid piperidin-4-ylmethyl ester.

5. A method of antagonizing the M_3 muscarinic acetylcholine receptor by administering to a subject in need thereof a safe and effective amount of a compound according to claim 1.

6. A method of treating a disease or disorder selected from the group consisting of chronic obstructive lung disease, chronic bronchitis, asthma, chronic respiratory obstruction, pulmonary fibrosis, pulmonary emphysema, and allergic rhinitis, irritable bowel syndrome, spasmodic colitis, gastroduodenal ulcers, gastrointestinal convulsions or hyperanakinesia, diverticulitis, pain accompanying spasms of gastrointestinal smooth musculature; urinary-tract disorders accompanying micturition disorders, neurogenic pollakisuria, neurogenic bladder, nocturnal enuresis, psychosomatic bladder, incontinence associated with bladder spasms or chronic cystitis, urinary urgency or pollakiuria, and motion sickness.

7. A pharmaceutical formulation comprising an active according to claim 1 and a suitable carrier.

8. A container containing a pharmaceutical formulation according to claim 1 fitted with a metering valve.

9. A device adapted for intranasal delivery of a pharmaceutical formulation comprising a container according to claim 8.